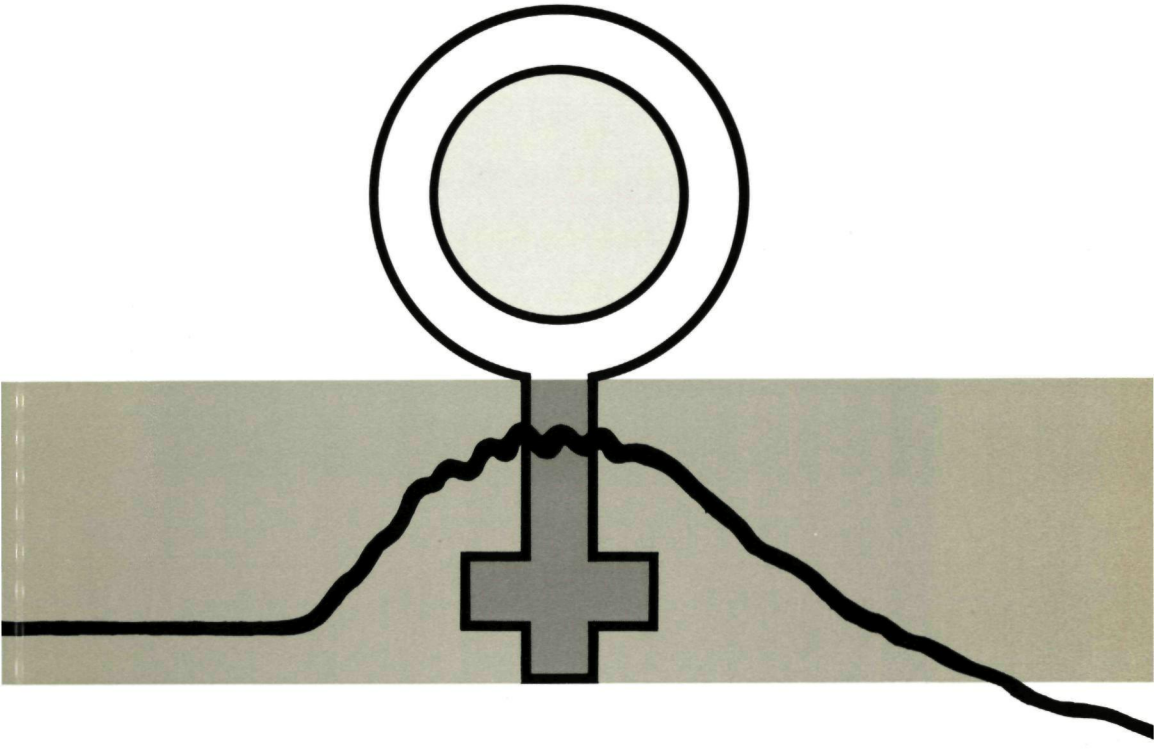
THE URETHRAL PRESSURE PROFILE IN CONTINENT WOMEN



J. M. van Geelen

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A prospective study during the use of oral contraceptives, the menstrual cycle, pregnancy and after delivery

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PROEFSCHRIFT

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Contents

List of abbreviations

AUL	=	anatomic urethral length
BBT	=	basal body temperature
CRL	=	crown rump length
CV	=	coefficient of variation
E_2	=	17β-estradiol
Fr	=	French (= 0.33 mm)
FSH	=	follicle stimulating hormone
FUL	=	functional urethral length
I.C.S.	=	International Continence Society
IP/10	=	integrated urethral closure pressure divided by 10
LH	=	luteinizing hormone
MUP	=	maximum urethral pressure
OC	=	low dose oral contraceptives
17-OH-P	=	17α-hydroxyprogesterone
P	=	progesterone
PMP	=	distance from internal meatus to the point of maximum urethral pressure
PTR	=	pressure transmission rate
RIA	=	radioimmunoassay
SD	=	standard deviation
SEM	=	standard error of the mean
TBP	=	total bladder pressure
UCP	=	urethral closure pressure
UPP	=	urethral pressure profile

In the female, the urethra as a whole acts as the urinary sphincter During continence, the intraluminal pressure within the urethra exceeds the total bladder pressure over almost the entire urethral length The urethral pressure profile denotes recording of the intraluminal pressure along the length of the urethra with the bladder at rest During the last two decades recording of the urethral pressure profile together with recording of total bladder pressure, i e , simultaneous urethrocystometry, has become a valuable tool in the assessment of urethral sphincter function and in differentiating between different forms of urinary incontinence

The aims of the present study were to investigate the biologic variability and the influences of hormonal alterations, pregnancy and delivery on the urethral pressure profile in healthy nulliparous women.

The urethral pressure profile is determined by the constituents within the urethral wall, by the properties of the periurethral structures and by its position within the pelvis Therefore, a short survey of the anatomy and neurophysiology of the lower urinary tract as well as a description of the urethral pressure profile and the variables measured, precedes the experimental part of the study

PART I

URINARY CONTINENCE IN WOMEN
GENERAL CONSIDERATIONS

Anatomy

1.1. INTRODUCTION

Three muscular systems are present in the wall of the bladder and urethra: the detrusor muscle, the trigonal muscle system and the smooth and striated urethral musculature. Since embryological studies have contributed significantly to the current concepts of the relationships and distinction between the muscle systems of the bladder and urethra, reference is made to the embryologic development in the description of the anatomy of the lower urinary tract.

The bladder and urethra act as a functional unit, whose purpose is the storage of urine in the bladder and its timely and complete expulsion per urethram under voluntary control. During the last two decades neurohistochemical and electronmicroscopic studies have further clarified the complex anatomic relationships between the muscular systems in the lower urinary tract and thus have provided a better understanding of the interaction between bladder and urethra in the mechanisms of continence and micturition.

1.2. EMBRYOLOGICAL CONSIDERATIONS

The bladder and urethra develop from the urogenital sinus. The point of entrance of the mesonephric ducts divides the urogenital sinus into the urethrovesical canal cranially, which gives rise to the urinary bladder and proximal urethra, and a phallic portion or the definitive urogenital sinus caudally, which in the female becomes the distal urethra and the vestibule of the vagina.

The epithelial lining of the bladder and urethra arises mainly from the urethrovesical canal, whereas the epithelium of the trigone and the proximal part of the posterior urethral wall develops from the invading mesonephric ducts. This initially mesodermal lining is gradually replaced by urogenital sinus epithelium (GYLLENSTEN, 1949). In the male, the endoderm of

the ventral wall of the definitive urogenital sinus proliferates and grows in caudal direction forming the urethral plate Along the caudal surface of the urethral plate parallel longitudinal folds extend from the mesenchyme around the cloaca and form the urethral groove The urethral folds finally close to form the penile urethra In the female, the growth of the definitive urogenital sinus falls behind Influenced by the caudal extension of the vaginal plate, the definitive urogenital sinus bends and widens in a ventro-dorsal direction The urethral folds line the opening of the urogenital sinus They remain unfused and eventually become the labia minora (DROES, 1972)

The detrusor muscle and most of the urethral musculature develop simultaneously but from separate mesenchymal anlagen in the 12th post conceptional week (6 cm CRL stage) The musculature of the trigone and dorsal urethral wall begins to differentiate from the mesodermal blastema at a later stage (11 - 20 cm CRL stage) and independently from the detrusor muscle (LOWSLEY, 1912, CHWALLA, 1927, DROES, 1974, KOIDE et al , 1979) By the end of the fifth month most of the differentiation of the urinary and genital tracts is concluded

1.3. DETRUSOR VESICAE

The detrusor muscle consists of a complex meshwork of interlacing large smooth muscle bundles embedded in loose connective tissue A detrusor muscle bundle consists of 12 to 15 individual muscle fibers surrounded by a collagen capsule The detrusor muscle bundles interconnect with other bundles by means of individual muscle fibers thus constituting a functional unit capable of producing a coordinated contraction By the end of the 14th postconceptional week the detrusor muscle is well developed except on the posterior side of the bladder base In neonates and at all subsequent ages a systematic arrangement of detrusor smooth muscle bundles in 3 layers can be observed This layering is most prominent in the region of the bladder neck

1 3 1 INNER LONGITUDINAL LAYER

Over most of the bladder the fibres of this layer are widely separated and run in many different directions On the ventral and lateral sides of the bladder neck, the inner fibres converge in a longitudinal direction and seem to continue as the inner longitudinal layer of the ventral and lateral urethral

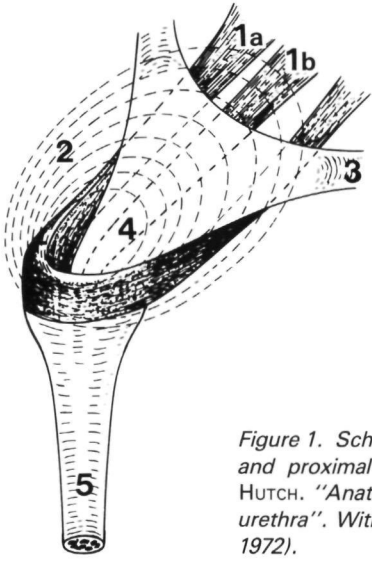
wall. In the posterior part of the bladder base, the continuity of the inner longitudinal layer is interrupted by the presence of the superficial layer of the trigone (KRANTZ, 1951; WOODBURNE, 1961; TANAGHO AND SMITH, 1966; BECK, 1969; VON HAYEK, 1969; HUTCH, 1972; DONKER et al., 1976).

1.3.2. MIDDLE CIRCULAR LAYER

In the distal part of the bladder circularly oriented smooth muscle fibres increase to form a prominent middle circular layer of almost concentrically arranged muscle bundles just above the level of the bladder neck (Heiss's rings or fundus ring) (HEISS, 1915; UHLENHUTH et al., 1952). The inner fibres of the middle circular layer encircle the bladder neck and fuse with the lateral edge of the deep trigone (Fig. 1) (TANAGHO et al., 1968-II). The anatomical structure composed of the fundus ring together with its fusion with the deep trigone has been called the "base plate" (HUTCH, 1972). The middle circular layer does not extend into the urethra but ends at the level of the internal urethral meatus.

1.3.3. THE OUTER LONGITUDINAL LAYER

The dorsomedial bundles of the outer longitudinal layer insert at the apex of the deep trigone at the bladder neck. The dorsolateral bundles proceed obliquely downward and forward and loop around the bladder neck and



1. *Outer longitudinal layer*
a. *Dorsolateral bundles*
b. *Dorsomedial bundles*
2. *Middle circular layer*
3. *Ureters*
4. *Deep trigone*
5. *Urethra*

Figure 1. Schematic representation of the female bladder neck and proximal urethra. (Redrawn and modified from J. A. HUTCH. *"Anatomy and Physiology of the bladder, trigone and urethra". With permission of Meredith Corporation, copyright 1972).*

the anterior aspect of the proximal urethra, forming the detrusor loop (Heiss, 1915, Wesson, 1920, Hutch, 1972) Thus, the detrusor muscle is delimited caudally by the detrusor loop The almost circular orientation of these fibres around the proximal urethra together with their direct continuity with the outer longitudinal layers of the detrusor probably plays an important role in the sphincteric mechanism of the urethra and at the initiation of micturition (Tanagho and Smith, 1966, Hutch, 1972) (Fig. 1)

1.4. TRIGONUM VESICAE

The musculature of the trigone and proximal urethra begins to differentiate from the mesodermal tissue independently from and at a later stage (i e , 11 - 20 cm CRL stage) than the detrusor muscle (Chwalla, 1927, Droes, 1974, Koide et al , 1979) Two layers can be discerned

1 4 1 THE SUPERFICIAL TRIGONE

The superficial inner layer consists of thin smooth muscle bundles and is the direct, sheet-like continuation of the inner longitudinal musculature of the intramural ureters These fibres converge at the internal meatus to proceed downward in the dorsal urethral wall (Wesson, 1920, Tanagho and Pugh, 1963, Woodburne, 1965, Bro Rasmussen et al , 1965, Hutch 1972, Itatani et al , 1977, Gosling, 1979)

1 4 2 THE DEEP TRIGONE

The deep trigone constitutes a compact, adherent structure consisting of fine, transversely oriented muscle fibres embedded in dense connective tissue According to Wesson (1920), Tanagho and Pugh (1963), Tanagho et al (1968 I) Nyo (1969) Hutch (1972) and Itatani et al (1977) the deep trigonal muscle develops as a direct continuation of the deep periureteral sheath Gosling (1979), however, considers the deep trigonal muscle to be the postero inferior extension of the detrusor muscle on the basis of its morphology, histochemistry and innervation The largest mass of deep trigonal muscle is situated in the base of the trigone Laterally the deep trigonal muscle fibers fuse with the muscle bundles of the middle circular layer of the detrusor muscle, and caudally the trigonal tissue extends into the dorsal wall of the urethra as a plate like continuation of transversally oriented smooth muscle fibers and collagenous tissue, ' the trigonal plate'' (Hutch, 1972, Droes, 1974, Huisman, 1979)

Muscle bundles of the ventral part of the deep trigonal mass encircle the internal urethral orifice and the upper quarter of the urethra, the "M Sphincter trigonalis" or "the trigonal ring" (Versari, 1897; Kalisher, 1900, Uhlenhuth et al , 1952, Mcneal, 1972, Droes, 1974, Huisman 1979) From its position and fiber orientation, the trigonal ring is the only anatomic structure that could be considered to be an internal urethral sphincter On its ventral and lateral sides the trigonal ring is covered by the detrusor loop, on its cranial edge by fibers of the middle circular layer of the detrusor

1 4 3 THE BLADDER NECK SPHINCTER MECHANISM

Under normal conditions, during the filling phase of the bladder, urine is retained at the level of the bladder neck The anatomic observations outli ned above demonstrate that the bladder neck and proximal urethra are composed of several smooth muscle systems, i e , the "trigonal ring", the "base-plate" composed of the deep trigonal muscle and fibers of the middle circular layer of the detrusor and the detrusor loop Together, these smooth muscle systems constitute the effective internal sphincter, also called proximal urethral or bladder neck sphincter mechanism The "trigo nal ring" constitutes the only true sphincteric structure around the bladder neck It is unlikely, however, that the "trigonal ring" contributes significantly to urinary continence as it represents only a small and relatively weak sphincteric structure (Huisman, 1979)

A concept of the functioning of the bladder neck sphincter mechanism was presented by Hutch (1972) As the bladder fills, the base of the bladder remains flat The circularly oriented muscle fibers of the middle circular layer pull the apex of the deep trigone inward so as to keep the bladder neck closed Outside the "base plate", the detrusor loop is so positioned that the apex of the deep trigone fits into its concave surface Since the detrusor loop continues into the posterior surface of the bladder as the right and left lateral posterior outer layer, it exerts a backward directed force in direct opposition to the "base plate", thus increasing the closure function of the bladder neck

At the initiation of voiding the base of the bladder moves out of its flat position and the bladder neck assumes a funnel shaped configuration (Lund et al , 1957) The funneling of the bladder outlet is associated with relaxation of the striated urethral and peri-urethral muscle and with a decrease in urethral pressure Contraction of the detrusor muscle further assists to augment the funneling of the bladder outlet and to keep the bladder neck open during voiding (Tanagho and Miller, 1970, Rud et al , 1979)

1.5. URETHRA

The urethral wall consists of mucosa, submucosa, two smooth muscle layers and a striated muscle layer. The smooth and striated urethral musculature develop during the same embryological period as the detrusor muscle, i.e., 6 cm CRL stage, but as an independent muscular system (CHWALLA, 1927; DROES, 1974; KOIDE et al., 1979). At all postnatal ages two smooth muscle layers and one outer layer of striated muscle can be discerned.

1.5.1. THE INNER LONGITUDINAL SMOOTH MUSCLE LAYER

In the dorsal urethral wall the inner longitudinal layer is continuous with the superficial trigone (TANAGHO et al., 1968-II; HUTCH, 1972; DONKER et al., 1976). On the ventral and lateral sides the inner longitudinal layer seems to be a direct continuation of the inner longitudinal layer of the detrusor.

1.5.2. THE CIRCULAR SMOOTH MUSCLE LAYER

The circularly oriented smooth muscle bundles of this layer surround the urethra on its ventral and lateral sides like a horseshoe. Dorsally the muscle bundles insert in the trigonal plate. The thickness of the circular smooth muscle layer is 6 to 8 times less than the inner longitudinal layer (HUISMAN, 1979). The longitudinal and the circular smooth muscle layers surround the urethra almost for its entire length. Distally the marked layering into two muscular coats is gradually lost and the smooth muscle bundles fan out in the periurethral connective tissue which surrounds the external meatus. The urethral smooth musculature constitutes a tough and compact tubular structure consisting of relatively small muscle bundles embedded in dense fibro-elastic collagenous tissue (Figs. 1.2 and 1.3).

1.5.3. THE STRIATED URETHRAL MUSCLE

Outside the smooth urethral musculature, circularly arranged striated muscle bundles surround the urethra. These fibers are most prominent on the ventral and lateral aspects of the urethral wall. Dorsally the fibers fuse with the transversally oriented tissue of the trigonal plate. The striated urethral muscle is most marked in the middle one-third of the urethral wall (Figs. 1.2 and 1.3). Cranially the striated fibers extend to the bladder neck and caudally the fibers fan out and end in the fascia superficialis of the uro-

genital diaphragm It follows that the striated urethral muscle is located above the urogenital diaphragm The intramural striated urethral muscle consists of small diameter, slow twitch, striated muscle fibers and is morphologically different and anatomically separate from the striated muscles of the pelvic floor (Von Hayek, 1960, Donker et al , 1976, Gosling et al , 1981) The smooth and striated elements of the urethral wall constitute the distal urethral sphincter mechanism or intrinsic urethral sphincter The term "external sphincter" often applied to the distal urethral mechanism is confusing as there is no direct connection between the intrinsic striated muscle in the urethral wall and the extrinsic or peri-urethral striated muscle in the pelvic floor

Compelling embryologic and histologic evidence indicates that the urethral smooth muscle is distinct from the detrusor muscle (Bulcke, van den, et al , 1970, Droes, 1974, Gosling, 1979) The two outer layers of the detrusor muscle do not continue in the wall of the urethra (Kalisher, 1900, Mcneal, 1972, Donker et al , 1976, Gosling, 1979, Huisman, 1979) In the adult, only the inner longitudinal layer on the ventral and lateral wall seems to be continuous with the inner detrusor layer Embryologically, however, these longitudinal bundles in the urethral wall do not belong to the detrusor muscle Kalisher (1900) and Huisman (1979) consider the entire urethral smooth musculature as a downward extension of the trigonal ring Uhlenhuth et al (1952) and Hutch (1972) concluded from their anatomic studies that the core structure of the urethra consists of trigonal tissue According to their views the deep trigone continues downward to form the major portion of the posterior urethral wall and the circular smooth muscle layer

The view that the detrusor and urethral musculature constitute anatomically distinct units is not uniformly accepted Krantz (1951), Lapides (1958), Bro Rasmussen et al (1965), Tanagho and Smith (1966), Woodburne (1968), Beck (1969), Von Hayek (1969) and Nyo (1969) argue on the basis of anatomical and histological studies in newborns and adults that the inner longitudinal and outer circular smooth muscle layers of the urethra are direct continuations of particular layers of the detrusor There is, however, no unanimity among these authors as to exactly which layers of the detrusor continue into the urethra

1.6 THE PERIURETHRAL STRIATED MUSCLES

The periurethral striated muscles of the pelvic floor encompass the urethra in its distal part at the level where the urethra traverses the urogenital di

aphragm and are separated from the intramural urethral muscle by a continuous connective tissue septum (Von Hayek, 1969; Donker et al., 1976; Gosling and Dixon, 1979; Huisman, 1979). The periurethral striated muscles contain large diameter fast twitch and slow twitch fibers which are functionally associated with rapid forceful muscle contraction (Von Hayek, 1960; Gosling et al., 1981).

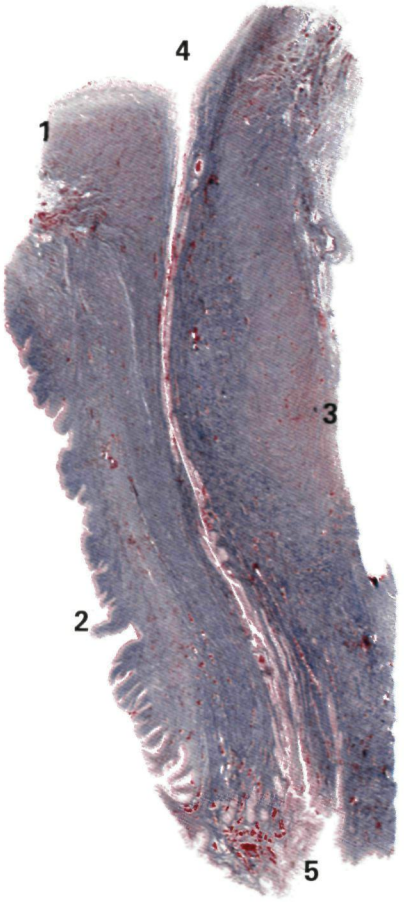


Figure 1.2.
Sagittal section of the adult female urethra:
1. deep trigone,
2. vaginal mucosa,
3. striated urethral muscle,
4. internal urethral orifice.
5. external urethral meatus.

1.7. THE PUBO-URETHRAL LIGAMENTS

The pubo-urethral ligaments constitute the suspensory mechanism of the urethra. From their apical attachment at the pelvic surface of the os pubis, the two posterior pubo-urethral ligaments run backwards and downwards as pyramid-shaped bands and fuse medially with the muscular coat of the urethra at its middle third. The single anterior pubo-urethral ligament attaches the distal urethra to the anterior surface of the symphysis pubis and extends as the suspensory ligament of the clitoris. Between the anterior and posterior pubo-urethral ligaments there is a slim collageneous structure known as the intermediate ligament. The pubo-urethral ligaments consist of dense parallel bundles of collagen fibers, smooth muscle bundles and cholinergic nerves. Their main function is to hold the urethra in its forwards and upwards position and to reduce its mobility during rise of intraabdominal pressure (ZACHARIN, 1963). The functional role of the pubo-urethral ligaments in the mechanism of continence is not clear (WILSON et al., 1979).

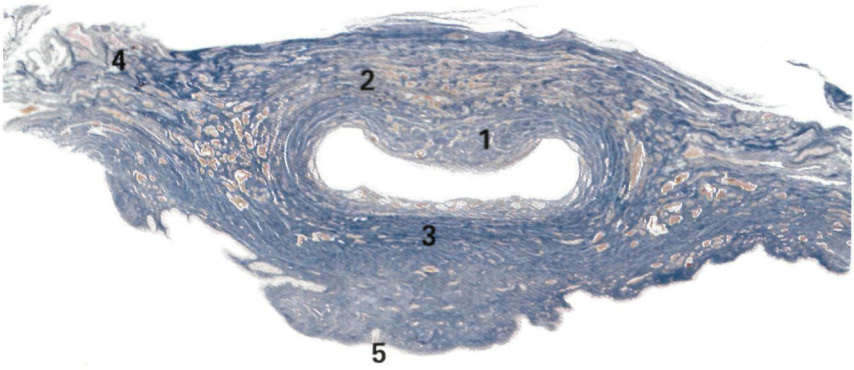


Figure 1.3. Transverse section of the urethra at the level of midurethra.
1. *inner longitudinal and outer circular smooth muscle,*
2. *striated urethral muscle,*
3. *trigonal plate,*
4. *periurethral striated muscle,*
5. *vaginal mucosa.*

CHAPTER 2

Neurophysiology

2 1. PERIPHERAL INNERVATION

2 1 1 INTRODUCTION

The function of the lower urinary tract is under control of both divisions of the autonomic nervous system The bladder and urethra are supplied by parasympathetic fibers by way of the pelvic nerves and by sympathetic fibers by way of the hypogastric nerves. Both the pelvic and hypogastric nerves are mixed nerves and contain motor or efferent fibers to and sen sory or afferent fibers from the bladder and urethra (KURU, 1965, NER GARDH, 1975, FLETCHER AND BRADLEY, 1978) There is no consensus as to the peripheral innervation of the striated urethral muscle The striated musculature of the pelvic floor receives its somatic afferent and efferent inner vation through the pudendal nerves

2 1 2 PELVIC NERVE

The pelvic nerve is the principal motor supply to the detrusor muscle The preganglionic fibers in this nerve originate in the intermediolateral cell co lumn in the sacral segments S_{2-4} of the spinal cord The preganglionic axons pass through the sacral ventral roots and pelvic nerves and synapse in the ganglia of the autonomic pelvic and vesical plexuses The distribution of the postganglionic terminal branches among the smooth muscle bundles is such that all muscle cells are supplied by one or more cholinergic nerves (EL BADAWI AND SCHENK, 1966, GOSLING AND DIXON 1975) In the human the density of the cholinergic nerves decreases distally in the bladder neck and in the urethra (EK et al , 1977b, KLUCK, 1979) These findings agree with the results of pharmacological studies and in vivo experiments which demonstate that in the human the contractile response evoked by pelvic nerve stimulation and parasympathicomimetic drugs is greatest in the bladder and moderate in the bladder base, whereas the cholinergic innervation of the urethral smooth musculature is of minor clinical importance In spite of the relatively rich supply of cholinergic nerves throughout

the human urethra, urethral pressure responses are hardly affected by cholinergic and anticholinergic drugs (Donker et al , 1972, Ek et al , 1977a, Ulmsten and Andersson, 1977, Ek et al , 1978) The exact neurotransmitter at the cholinergic nerve terminals in the bladder is still unknown at the present time Atropine partially antagonizes the muscarinic response at the neuroeffector junction (Ambache and Aboo Zar, 1970) Recent observations suggest the presence of a second non cholinergic neurotransmitter, most probably purinergic in nature, at the neuroeffector sites in the mammalian bladder (Eaton et al , 1981)

2 1 3 HYPOGASTRIC NERVE

The preganglionic sympathetic fibers to the lower urinary tract stem from the nucleus intermediolateralis in the thoracolumbar segments T10 - L2 The majority of the sympathetic fibers pass through the splanchnic nerves and most of them synapse in the ganglia of the superior hypogastric plexus The pre- and postganglionic sympathetic fibers continue in the hypogastric nerves and terminate in the ganglia of the pelvic and vesical plexuses Some of the postganglionic sympathetic fibers accompany the blood vessels in the pelvis and in the wall of the bladder and urethra, while others have been described as terminating on the vesical and urethral smooth muscle Still other postganglionic sympathetic fibers terminate on the postganglionic parasympathetic neurons (see 2 1 4 and 2 1 5)

2 1 4 THE PELVIC PLEXUS

The preganglionic parasympathetic fibers in the pelvic nerves and the pre and postganglionic sympathetic fibers in the hypogastric nerves form the pelvic plexus which is situated lateral to the rectum , uterus and vagina Ganglia of the pelvic plexus extend as the vesical plexus to the posterior part of the bladder neck and into the lateral bladder wall From the pelvic plexus postganglionic terminal branches supply the bladder, urethra, vagina, rectum and anus The ganglion cells of the pelvic and vesical plexuses are of three types exclusively adrenergic, exclusively cholinergic, and postganglionic neurons responding to stimulation of either sympathetic or parasympathetic preganglionic input (Bradley and Teague, 1968) Transmission at the parasympathetic ganglia of the urinary bladder is cholinergic Histofluorescence studies have shown that parasympathetic ganglion cells in the pelvic plexus also receive synaptic terminals from postganglionic adrenergic neurons (Hamberger and Norberg, 1965, El Badawi

AND SCHENK, 1966, KLUCK, 1982) Noradrenaline released from the postganglionic adrenergic synaptic endings may thus interfere with the cholinergic transmision in the parasympathetic ganglia (DE GROAT AND SAUM, 1971) The complex organization of the pelvic ganglia provides for functional interaction of sympathetic and parasympathetic nervous systems in the innervation of the lower urinary tract

2 1 5 THE URINARY BLADDER

The number and distribution of noradrenergic nerves among the detrusor smooth muscle bundles is sparse compared to the rich and uniform supply of parasympathetic fibers (NERGARDH AND BOREUS, 1972, EK et al , 1977b, GOSLING et al , 1977, KLUCK, 1979) The adrenergic fibers which can be demonstrated usually accompany the vascular supply and run in the connective tissue which separates the smooth muscle bundles SUNDIN et al (1977) and BENSON et al (1979) observed thin, varicose adrenergic fibers running parallel to the detrusor smooth muscle bundles These fibers were separate from the adrenergic fibers accompanying the bloodvessels The morphological findings in the human bladder are in agreement with those observed in other species (EL BADAWI AND SCHENK, 1966, RAEZER et al , 1973, NERGARDH, 1975, GOSLING AND DIXON, 1975, NORLEN et al , 1976, KLUCK, 1982)

2 1 6 BLADDER OUTLET AND URETHRAL SMOOTH MUSCLE

GOSLING et al (1977) and NORDLING AND CRISTENSEN (1978) observed a very sparse distribution of noradrenergic nerves among the smooth muscle bundles in specimens obtained from the female bladder neck and proximal urethra The distribution of noradrenergic nerves was similar in pattern to that observed in other parts of the detrusor muscle SUNDIN et al (1977) and EK et al (1977b), on the other hand, found a distinct and rich noradrenergic nerve supply in the trigone area and posterior bladder neck and a sparse but uniform distribution of adrenergic nerves throughout the entire human urethra KLUCK (1979), using a slightly different technique, observed a clear but sparse noradrenergic plexus in the posterior bladder neck whereas the urethral smooth muscle was almost devoid of noradrenergic fibers Adrenergic endings, however, were present in the ganglia located in the adventitia of the bladder wall Taken together, the studies mentioned above differ with regard to the density of the sympathetic innervation of the bladder neck and trigone area, but all studies indicate a scanty adrenergic innervation of the urethra In contrast to the findings in

the female, in the male the smooth muscle bundles around the proximal urethra constitute a sphincteric structure which is richly supplied with noradrenergic nerve fibers (Gosling et al , 1977)
These findings in man differ considerably from those obtained in other species where a rich supply of adrenergic terminals in the bladder outlet and in the urethra can be observed (Raezer et al , 1973, El Badawi and Schenk, 1974, Gosling and Dixon, 1975, Kluck, 1982) The conflicting results with regard to the distribution of noradrenergic nerves in the lower female urinary tract may be attributable, in part at least, to differences in methodology It is also reasonable to suppose that there are differences in density and distribution of noradrenergic fibers and receptor sites in the lower urinary tract between different species and even between individuals of the same species (Nergardh, 1975, Gosling et al , 1977, Kaneko et al , 1980) In addition, the density of the adrenergic nerves decreases with in creasing age (Benson et al , 1979)

2 1 7 URETHRAL STRIATED MUSCLE

Controversy exists as to the peripheral innervation of the urethral striated muscle The anatomic dissections of Gilvernet (1964), Donker et al (1976) and Gosling and Dixon (1977) indicate that the intramural striated urethral muscle receives its motor innervation through branches of the pelvic nerve The pelvic nerve, thus, carries not only autonomic nerves to the detrusor and urethra but also somatic fibers to the intramural striated muscle By means of histochemical techniques El Badawi and Schenk (1974) demonstrated a triple innervation, i e , sympathetic-parasympathetic-somatic innervation of the external urethral sphincter (authors' term) Wein et al (1979), however, found no evidence for adrenergic innervation of the external urethral sphincter
Using the technique of retrograde axonal transport of horseradish peroxidase, Tanagho et al (1982) concluded that the somatic innervation of the urethral striated muscle is supplied by the pudendal nerve

2 1 8 COMMENT

The adrenergic nerves in the lower urinary tract are most often observed in connection with blood vessels, mainly arteries, in the muscularis and submucosa There is an appreciable vascular component in the production of intraurethral pressure at rest (Rud et al , 1980) However, changes in urethral closure pressure as a result of sympathetic stimulation are me diated not through the changes in calibre of the blood vessels, but directly

through the smooth muscle of the urethral wall (Donker et al , 1972, Taira, 1972, Tulloch, 1974, Nordling et al , 1981a) These observations indicate that the influence of the sympathetic nervous system on the function of the lower urinary tract is mediated through effects on smooth muscle in the bladder and urethral wall

The relatively sparse distribution of noradrenergic nerves in the human lower urinary tract observed in morphological studies seems inconsistent with the evidence obtained from studies in experimental animals and from clinical studies in man which demonstrate an important role of the sympathetic nervous system in the functional control of bladder and urethra (Kleeman, 1970, Donker et al , 1972, Krane and Olsson, 1973 I and II, Ek et al , 1977a, Caine, 1977, Nordling et al , 1981b) In man both alpha and beta-adrenergic receptors are present in bladder and urethra Beta-adrenergic (i e , relaxation mediating) receptors predominate in the detrusor muscle (Nergardh and Boreus, 1972, Awad et al , 1974) Alpha adrenergic (i e , contraction-mediating) receptors predominate in the bladder base, bladder neck and in the urethra (Nergardh and Boreus, 1972, Awad et al , 1974, Sundin et al , 1977) The increased sympathetic activity recorded during the storage phase acts to promote bladder filling and simultaneously increases urethral resistance by stimulation of the alpha adrenergic receptors in the bladder base and proximal urethra (Edvardsen, 1968, Bradley and Teague, 1969, Tulloch, 1975)

The actual role of the adrenergic system in bladder control is undoubtedly more complex than the simple model suggested in the foregoing paragraph Benson et al (1975) demonstrated on muscle strips of canine bladder body that the response of the detrusor muscle strips to sympathetic stimulation was determined by the tension within the muscle bundles At high degree of detrusor stretch the relaxation response to norepinephrine (beta effect) was progessively converted to a contractile response (alpha-effect) Nergardh (1975) observed that the type of reaction of the smooth muscle in the bladder outlet was dependent upon the concentration of released noradrenaline at the neuromuscular junction In low concentrations adrenaline and noradrenaline relax the bladder outlet whereas high concentrations of these catecholamines contract the same region Nergardh and coworkers (1977) also observed that in the human bladder the β-receptors had neither β_1 nor β_2 characteristics It was suggested that the β receptors in the human bladder are of a third type The presence of interganglionic connections between the adrenergic and cholinergic systems and the findings cited above of noradrenergic synaptic terminals on the postganglionic cholinergic neurons in the region of the

bladder outlet suggest that modulation of neurotransmission at the ganglionic level influences the regulatory role of the autonomic system on the function of the lower urinary tract (De Groat and Saum, 1971) In addition to the cholinergic and adrenergic fibers in the lower urinary tract, Alm et al (1979) demonstrated the presence of peptidergic nerves in the human urinary tract The occurrence and distribution pattern suggest that peptidergic nerves participate in the regulation of smooth muscle activity
Estrogens influence smooth muscle function (Batra, 1980) In addition to the effects mediated through intracellular receptors, gonadal steroids also influence smooth muscle activity by modifying the adrenoceptor response Estrogens increase alpha-adrenergic sensitivity, whereas progesterone enhances the beta-adrenergic response (Raz et al 1972a, Raz et al , 1973, Roberts et al , 1977)

2.2. CENTRAL NERVOUS SYSTEM ORGANIZATION

2 2 1 INTRODUCTION

The interaction of the continence mechanism and the micturition process involves a number of coordinated reflexes operating between the detrusor, the urethra and the striated musculature of the pelvic floor on one hand and the reflex centers in the sacral spinal cord and in the brainstem reticular formation on the other hand (Kuru, 1965, Fletcher and Bradley, 1978)

2 2 2 AFFERENT PATHWAYS

Sensory receptors in the bladder and urethra are present as free and unspecialized nerve endings Proprioceptive impulses resulting from bladder distention and detrusor contraction are mediated primarily via the pelvic nerves and reach the sacral spinal cord through the third and fourth sacral dorsal roots The sensory innervation of the urethral striated muscle and of the striated muscle of the pelvic floor consists of muscle spindles and tendon organs Impulses resulting from changes in tonus of the striated muscles are transmitted via the pelvic and pudendal nerves and reach the sacral spinal cord through the second, third and fourth dorsal roots (Bradley et al , 1973, Gosling and Dixon, 1974, Bradley et al , 1974) Exteroceptive modalities such as pain, touch and temperature are transmitted from the sensory endings in the mucosa and submucosa and conveyed through both the pelvic and hypogastric nerves
The most important factor in the initiation of micturition is bladder dis-

tension The sustained contraction of the detrusor necessary for complete evacuation of the bladder is dependent on the tension receptors that are excited by the contraction of the detrusor itself Because the individual sensory receptors vary greatly in excitation threshold, the afferent system can transmit impulses over a wide range, with different receptors being recruited at different levels of pressure (KURU, 1965, FLETCHER AND BRADLEY, 1978) The efferent pathways are described under 2 1 2 and 2 1 3

2 2 3 CENTRAL PATHWAYS

The afferent fibers of the pelvic and pudendal nerves synapse on interneurons and projection neurons situated in, respectively, the dorsal and ventral parts of the intermediolateral nucleus Interneurons may synapse on efferent neurons on the ipsilatereral or contralateral side at the same segmental level or may ascend to synapse bilaterally on sympathetic preganglionic neurons The complex network of interneuronal connections together with recurrent inhibition at the level of the lumbosacral segments provides for a number of spinal reflexes (BRADLEY AND TEAGUE, 1968, BRADLEY, 1969, MAHONY et al , 1977) The importance of this segmental organization becomes evident in patients with spinal cord injury
In addition to the short neural pathways, a number of long neural tracts, both ascending and descending, mediate the influence of higher central nervous system centres on the mechanisms of continence and micturition (NATHAN AND SMITH, 1958, ANDREW AND NATHAN, 1965, KURU, 1965, BRADLEY et al , 1974) For purposes of clinical application, BRADLEY AND COWORKERS (1974) introduced a concept of the central nervous system organization of the normal micturition reflex into four distinct neuroanatomic circuits or loops

I Cerebral cortex brainstem reticular formation This circuit consists of fiber systems from the frontal lobe to the pontine mesencephalic reticular formation The subcortical nuclei and the cerebellum provide additional input This loop coordinates the volitional control of the micturition reflex

II Brain stem - sacral spinal cord The afferent pathway consists of detrusor sensory axons which travel in the spino reticular or sacro-bulbar tract to synapse in the lateral part of the brainstem reticular formation The descending pathway consists of efferent axons originating in the nuclei of the reticular formation, which travel in the lateral reticulospinal tract to terminate on the detrusor motor neurons in the sacral

spinal cord. This loop provides for a sustained detrusor contraction of adequate temporal duration to complete total evacuation of the intravesical contents.

III. Detrusor - sacral spinal cord - striated muscles of the pelvic floor· Detrusor sensory afferents terminate either directly or through internuncial neurons on the pudendal motor neurons in the ventral gray horn The spinal reflex circuit between sensory afferents and pudendal motor neurons provides for coordination between detrusor contraction and depression of pudendal nerve activity with resultant relaxation of the striated musculature around the urethra and in the pelvic floor.

IV. Cerebral cortex - sacral spinal cord· Impulses, constantly generated from the muscle spindles and tendon organs in the pelvic floor pass directly, without synapsing, in the posterior column of the spinal cord to the medulla oblongata and project ultimately to the sensorimotor cortex of the frontal lobe. The efferent axons travel in the pyramidal tracts from this cortical area to the pudendal motor neurons in the sacral spinal cord This cortico-spinal tract provides for the volitional control of the activity of the striated urethral and periurethral muscles in the pelvic floor. Micturition is initiated by relaxation of the striated musculature in the pelvic floor as can be demonstrated by sphincter electromyography from the urethral and anal sphincters

The urethral pressure profile

3 1 INTRODUCTION

The term "urethral pressure profile" (UPP) denotes a recording of the intraluminal pressure exerted by the urethral wall on a pressure measuring device as it is withdrawn from the bladder to the external meatus with the bladder at rest Under normal conditions, during the filling phase of the bladder, the urethral lumen is closed and continence is maintained at the level of the bladder neck (Ardran et al , 1956, Caine and Edwards, 1958, Jeffcoate, 1965, Turner Warwick, 1976) The intraluminal pressure within the urethra exceeds the bladder pressure over almost the entire urethral lenght (Enhorning et al , 1964)

Stimulated by the clinical problems encountered in the differential diagnosis and treatment of urinary incontinence, the interest in studying urethral function by determining the urethral pressure profile has grown Several techniques to record the urethral pressure profile have been developed during the last two decades

1 perfusion techniques utilizing constant water flow (Lapides et al , 1960, Brown and Wickham, 1969)
2 perfusion techniques utilizing gas or carbon dioxide (Robertson,1974, Raz and Kaufman, 1976)
3 fluid filled balloon catheters with the pressure transducer located out side the urethra (Simons, 1936, Hodgkinson, 1960, Enhorning, 1961, Donker et al , 1972, Tanagho and Jonas, 1977)
4 pressure transducers placed intraluminally (Karlsson, 1953, Shelly and Warrell, 1965, Asmussen and Ulmsten, 1975)

Techniques for simultaneous recording of intravesical and intraurethral pressures were introduced by Karlsson, 1953, Hodgkinson, 1960 and Enhorning, 1961 Recent technical advances have improved the recording equipment Microtransducers embedded in a thin semiflexible catheter are now available which allow accurate and reliable measurements of the intra

vesical and intraurethral pressure under both static and dynamic conditions With the aid of a mechanical withdrawal apparatus it is possible to record the intraurethral pressure in relation to the intravesical pressure at every point throughout the urethra from the bladder neck to the external meatus By subtraction the difference between maximal urethral pressure and total bladder pressure, i e , urethral closure pressure, can be calculated

The clinical value of urethral pressure profile in diagnosing lower urinary tract disorders has been and still is the subject of many studies ENHORNING (1961) first performed simultaneous measurements of intravesical and intraurethral pressures at rest and under dynamic conditions in normal women, in women suffering from stress incontinence and in puerperas Since then, a great number of investigators, using different recording techniques, have assessed the diagnostic value of urethral pressure profile measurements for differentiation between different forms of urinary incontinence and to study the pathofysiology of lower urinary tract disorders All have confirmed or modified the results obtained by ENHORNING In general, the results of these studies may be summarized as follows
Under normal conditions the intraurethral pressure exceeds total bladder pressure over almost the entire urethral length Maximum urethral pressures at rest are generally measured 1 to 1 5 cm from the urethrovesical junction Maximum urethral pressure and urethral length show a tendency to decrease with increasing age In women suffering from stress incontinence the mean maximum urethral pressure at rest is significantly lower for all the 10 year age groups from 30 to 69 years than for the asymptomatic women of the same age The mean urethral length is generally shorter in women with stress incontinence than in normal subjects of the same age The maximum urethral pressure recorded in women on the sixth day after vaginal delivery was significantly lower than that of normal non puerperal women
The urethral vascular bed probably plays an important auxiliary role in urethral closure mechanism Vascular pulsations are generally observed in the urethral wall of normal women The amplitude of these pulsations is smaller than normal in puerperas whereas in women with stress incontinence vascular pulsations usually can not be measured
The proximal part of the urethra is located above the pelvic floor In asymtomatic women changes in intraabdominal pressure are transmitted to the bladder and almost to the same extent to the intrapelvic segment of the urethra In women with stress incontinence transmission of increased

intraabdominal pressure to the urethra is deficient resulting in a sustained decrease in urethral closure pressure during stress

3.2. DEFINITIONS OF URETHRAL PRESSURE PROFILE VARIABLES

Simultaneous urethrocystometry including measurement of the urethral pressure profile provides recording of the following parameters of urethral function Definitions are according to the Standardization Committee of the International Continence Society (ICS) (Bates et al , 1977)

- Functional urethral length (FUL), the length of the urethra along which the intraurethral pressure exceeds the total bladder pressure
- Anatomic urethral length (AUL)· the distance between the point in the urethra where intraurethral pressure exceeds the total bladder pressure and the point where the intraurethral pressure falls to atmospheric pressure
- Bladder pressure or total bladder pressure (TBP) pressure within the bladder in relation to atmospheric pressure
- Maximum urethral pressure (MUP) the maximum pressure of the urethral pressure profile recorded in relation to the atmospheric pressure
- Urethral closure pressure (UCP) the difference between maximum urethral pressure and the simultaneously measured total bladder pressure
- Point of maximum urethral pressure (PMP) distance from the internal meatus to the point of maximum urethral pressure
- Integrated pressure (IP/10) surface of the area between the urethral pressure curve and the bladder pressure level, divided by 10

These definitions are further illustrated in Figure 4 2

3.3 FACTORS DETERMINING THE URETHRAL PRESSURE PROFILE AT REST

The urethral pressure profile represents a composite of the pressures produced by all of the components that are present in the urethral wall, i e , the inner urethral wall composed of mucosa and submucosa, the smooth and striated urethral muscle, its binding fibro elastic tissue and the

periurethral striated muscle The contribution of each component individually to the maintenance of the urethral closure pressure and their roles in the continence mechanism are not clear

3 3 1 THE INNER URETHRAL WALL

The urethral muscosa and submuscosa constitute a compressible and easily deformable layer (ZINNER, 1976) The spongy structure of this highly vascularized layer will under external compression ensure complete occlusion of the urethral lumen (VON HAYEK, 1969, ZINNER et al , 1980)

3 3 1 1 MUCOSA

The epithelial lining in the distal third of the urethra consists of stratified squamous epithelium More proximally the urethral epithelium gradually changes to pseudo-stratified cylindrical epithelium in the middle third and to transitional epithelium in the bladder neck and in the bladder (HUISMAN, 1979) Cytologic changes similar to those found in vaginal epithelial cells are observed in the urethral epithelium during the reproductive cycle These changes result from differing levels of estrogen activity, both during the menstrual cycle and from menarche to the reproductive years and postmenopause (SMITH, 1972)

3 3 1 2 SUBMUCOSA

This layer consists of a loose areolar stroma in which a great number of large thin walled venous sinuses surrounding the urethral lumen for its entire length can be observed BERKOW (1953) and HUISMAN AND SALOME (1977) pointed out that the blood supply and the number of venous sinuses in the urethral wall is excessive in relation to the metabolic activitity of this tissue The vascular bed is most prominent at midurethra where the vessels have thinner walls and where a rich system of anastomoses between arterial and venous vessels exists The urethral vascular bed is most fully developed in the reproductive period and declines postmenopausally (HUISMAN, 1979) RAZ et al (1972b) and RUD et al (1980) as well as the exsanguination experiments by TULLOCH (1974) indicate that the urethral vascular bed contributes considerably (up to 30%) to the total intraurethral pressure Estrogens cause vasodilation and increased vascular pulsations in the urethral vascular bed (MOLNAR AND NAGY, 1965, VAN GEELEN et al , 1981, Chapter 6) It seems reasonable to infer that the beneficial effect of estrogens on urethral closure function is to a great extent attributable to their effects on the urethral vascular bed

3 3 2 THE URETHRAL SMOOTH MUSCLE

The anatomic structure of the bladder neck and proximal urethra is composed of several smooth muscle systems which together constitute the effective internal sphincter mechanism (see Chapter 1) The normal bladder neck is competent, cough proof and strain proof and maintains continence without the assistance of the sphincter mechanism distal to it (Turner Warwick, 1976, Mcguire and Wagner, 1977) Passive continence is thus to a great extent maintained by the tonus of the smooth muscle systems at the bladder neck together with the tension produced by the fibroelastic tissue surrounding the smooth muscle bundles (Woodburne, 1961 Khanna et al , 1981)

The distal urethral sphincter is composed of the urethral smooth muscle layers and the striated urethral and periurethral muscle Pharmacological experiments and clinical studies indicate that the innervation of the bladder neck and urethral smooth muscle is mediated mainly by alpha adrenergic receptors The parasympathetic innervation seems of minor importance for urethral closure function The contribution of the smooth muscle component together with its binding fibroelastic elements to the resting urethral closure pressure varies according to different investigators and ranges from 40 to 80% (Tanagho et al , 1969-I, Donker et al , 1972, Awad and Downie, 1976, Rud et al , 1980)

3 3 3 THE URETHRAL STRIATED MUSCLE

The striated component of the urethra consists of the intrinsic urethral and the extrinsic periurethral striated muscles These latter are part of the pelvic floor Anatomic and neurohistochemical studies have demonstrated morphological differences and differences in innervation between the urethral striated muscle and the periurethral striated muscles These observations suggest different functional activity of these separate components The small diameter slow twitch fibers of the urethral striated muscle are functionally capable of maintaining tone over prolonged time periods without fatigue, whereas the large diameter fast twitch and slow twitch fibers of the striated muscle of the pelvic floor allow for rapid, forceful muscle contraction

Information as to the influence of the striated muscle component on intraurethral resistance is not consistent In dogs, Cass and Hinman(1968) and Awad and Downie (1976) found that blockade of striated muscle activity did not significantly influence urethral pressures Also in dogs, Tanagho et al (1969 II) and Koff (1977) observed considerable decreases in intra

urethral resistance, 50% and 42% respectively, after striated muscle paralysis by tubocurarine. In the human female, LAPIDES et al. (1960) found a considerable decrease in intraurethral resistance at the level of the mid-urethra during spinal anesthesia, whereas DONKER et al. (1972) observed only minimal changes after striated muscle paralysis. MCGUIRE AND WAGNER (1977) observed that complete sacral denervation did not markedly change the urethral pressure profile except for a decrease in peak profile in the zone most closely related to the pelvic floor musculature. RUD et al., (1980) estimated the contribution of the striated component to urethral closure pressure at rest approximately 30%. The anatomic location and the fiber characteristics of the striated muscles of the pelvic floor seem ideally suited to increase urethral resistance during those events which cause sudden increase in intraabdominal pressure (e.g. coughing, sneezing) and during voluntary interruption of micturition.

3.4. FACTORS DETERMINING THE URETHRAL PRESSURE PROFILE DURING STRESS

The proximal two-thirds of the urethra is located within the pelvic cavity above the urogenital diaphragm. Ventrally the urethra is attached to the symphysis pubis by the pubo-urethral ligaments. Dorsally, the urethra is supported along its course on the anterior vaginal wall by the levator ani muscles. Increased intraabdominal pressure is transmitted from the abdominal cavity to the bladder and urethra and through the urethral wall to the urethral lumen. From the topography of the pelvic organs one would expect the intraabdominal pressure rise to be transmitted equally to the bladder and to the intrapelvic segment of the urethra. However, even in asymptomatic women, transmission of pressure to the bladder and intrapelvic urethra is not equal and the pattern of transmission differs between normal subjects. Several investigators observed in some women that transmission of intraabdominal pressure during stress resulted in an increase in urethral pressure which exceeded the increase in total bladder pressure, thus resulting in an increased urethral closure pressure. (Positive pressure transmission ratio or positive PTR). (ENHORNING, 1961; RUD, 1980a; CONSTANTINOU AND GOVAN, 1980; FAYSAL et al., 1981). In other normal subjects transmission of raised intraabdominal pressure gradually decreased from the bladder neck towards the external meatus thus resulting in a decrease in urethral closure pressure (negative PTR). (ENHORNING, 1961; TOEWS, 1967; BUNNE AND OBRINK, 1978; HEIDLER et al., 1979; RUD,

1980a, HILTON AND STANTON, 1982a) Also in asymtomatic primigravid women different responses of the urethral closure pressure to stress could be observed (VAN GEELEN et al , 1982, chapter 7) The decrease in urethral closure pressure during stress observed in continent women generally was not continuous along the entire urethral length and an increase in urethral closure pressure was often observed in the distal urethral segment This distal response to stress preceded in time and exceeded in pressure the other pressure changes in the bladder and proximal urethra (ENHORNING, 1961, CONSTANTINOU AND GOVAN, 1980, RUD, 1980a, VAN DER KOOI et al , 1982) Similar changes in urethral response to stress were observed in dogs (THUROFF et al , 1982)

These observations indicate that the urethral response to stress does not merely represent passive transmission of raised intraabdominal pressure but also involves, al least in the distal third of the functional urethra, an additional component, presumably active contraction of the striated muscles of the pelvic floor This active mechanism magnifies the urethral pressure response and thus constitutes a secondary defence mechanism during stress

Transmission of pressure to the bladder and intrapelvic urethra is governed by the anatomic position of these organs within the pelvic cavity and by the properties of the supporting tissue of the pelvic floor Dislocation of the urethra, e g , in prolapse of the anterior vaginal wall, dislocation of the bladder during stress and scarring of the urethral and periurethral tissue, may all impair proper transmission of pressure The differing responses observed in healthy nulliparous women indicate that constitutional weakness of the supporting tissues in the anterior vaginal wall and in the pelvic floor may play a role as well

In women suffering from stress incontinence transmission of pressure to the proximal urethra is deficient and the decrease in urethral closure pressure (negative PTR) along the urethra during stress is significantly greater than the decrease observed in continent women In addition, the active response to stress in the distal part of the functional urethra is usually absent (ENHORNING, 1961, HEIDLER et al , 1979, HILTON AND STANTON, 1982b)

3 5 SUMMARY

In spite of the differing opinions which still exist with regard to some aspects of the anatomy and innervation of the bladder neck and urethra, it is generally agreed that the closure function of the bladder neck and proximal urethra is determined by the tonus of the sympathetically inner-

vated smooth muscle bundles together with the inherent tension exerted by the binding fibroelastic tissue At midurethra and in the distal part of the functional urethral length the urethral smooth muscle combines with the urethral and periurethral striated muscle systems to maintain adequate urethral closure pressure The inner urethral wall, composed of mucosa and submucosa, probably plays an important auxiliary role in the continence mechanism by producing a watertight seal within the lumen of the urethra

Increased intraabdominal pressure is transmitted to the bladder and almost to the same extent to the proximal urethra The major function of the striated component seems to be to reinforce urethral closure pressure during stress and during voluntary interruption of micturition The observations outlined in this chapter lead one to conclude that the resting urethral closure pressure, the transmission of increased intraabdominal pressure to the bladder and urethra and the contractility of the striated muscles in the pelvic floor combine to maintain urinary continence both at rest and under stress Thus, recording of the urethral pressure profile under static and dynamic conditions is valuable in the assessment of urethral sphincter function and in the differentiation between different forms of urinary incontinence (TANAGHO, 1979)

PART II

OWN INVESTIGATIONS

Subjects and materials

4.1. INTRODUCTION

Several techniques to record pressures in vivo are presently available: open catheter systems, fluid filled balloons, membrane catheters and microtransducer catheters. Studies comparing the reliability of the various techniques for recording urethral pressure profiles have given inconsistent results (Schmidt et al., 1977; Jonas and Klotter, 1978; Teague and Merrill, 1979; Evans et al., 1979).

Until recently the open catheter perfusion system has been most commonly used for recording the urethral pressure profile (Brown and Wickham, 1969). The open catheter perfusion system measures the resistance presented by the wall of the tubular structure to flow output from one or more openings in the catheter together with the pressure needed to maintain a constant flow within the system. The accurary and reliability of the open catheter system for pressure recording within the lower urinary tract as well as in the anal canal have been well documented (Griffiths, 1980; Kuijpers, 1981). An important disadvantage in routine measurement of the urethral pressure profile with a perfusion catheter is the slow response of the system to increasing pressures (Abrams et al., 1978).

Asmussen and Ulmsten (1975) introduced a new technique for intraurethral pressure recording using a stable ultraminiature pressure transducer enclosed in a thin semiflexible catheter. This technique measures directly the compressive force of the urethral wall on the transducer membrane as it is withdrawn through the urethra. The microtransducer technique has proven to be an accurate and sensitive technique with a high frequency response. The measurements are not influenced by inaccuracies inherent in a fluid filled or gas perfused system such as delayed response time, damping due to air bubbles, and leakages. In addition, the small diameter of the catheter minimizes urethral distortion.

The reliability and accuracy of the microtransducer technique has been extensively studied and compared with other pressure recording techniques both in the experimental model and *in vivo* (Asmussen, 1975; Furrer and

EBERHARD, 1977; ERLANDSON AND FALL; 1978; TEAGUE AND MERRILL, 1979).
If the system is properly calibrated, measuring inaccuracies due to instrumental errors should be minimal. Thus, the variability of the urethral pressure profile recordings, made with the microtransducer technique and performed according to a precise and standardized methodology is mainly determined by biological variables and physiologic alterations.

The aims of the present study were to investigate the effects of biologic variables and the influences of physiologic changes in healthy women on the urethral pressure profile. All studies were performed in asymptomatic nulliparous women, between 18 and 35 years of age, according to a standardized methodology. None was suffering from any symptoms related to the lower urinary and genital tracts and none had a history of previous genito-urinary operations. Prior to the study all women were informed of the aims of the study and of the methodology to be applied. All gave informed consent. The factors studied were:

Chapter 5
a. short term and long term reproducibility;
b. effects of axial rotation of the recording catheter;
c. effects of low dose oral contraceptives;
d. postural changes and dynamic effects.

Chapter 6 the relationship between hormonal changes during the normal menstrual cycle and changes in the urethral pressure profile.

Chapter 7 the influence of pregnancy and delivery on the variables of the urethral pressure profile in healthy nulliparous women.

Those elements which are common to all studies, i.e., the measuring device, measuring technique, and determination of hormone levels in serum, are described in this chapter (chapter 4), preceding the reports of the three studies. The study population and those elements of methodology which were specific to a particular study, including the statistical methods employed, are described in the relevant chapters. Each of the chapters 5, 6 and 7 represents a complete and separate study with specific aims. For this reason the results and the related discussion are presented together within the same chapter.

4.2. METHODOLOGY

4.2.1. MEASURING DEVICE

The microtransducer catheter consists of two silicon strain gauge pressure sensors which are mounted at 6 cm distance from each other in a semi-

flexible dacron catheter (Millar Instruments Inc , Houston, Texas) The proximal pressure sensor is located at 6 cm from the tip where the catheter has an outer diameter of 7 Fr (2 33 mm) The distal microstransducer is at the tip of the catheter, where the outer diameter is 5 Fr (1 65 mm) During a recording session the distal pressure sensor is situated in the bladder and registers the intravesical pressure whereas the proximal pressure sensor is withdrawn through the urethra, recording the urethral pressure profile The difference between urethral pressure and bladder pressure, i e , the differential pressure or urethral closure pressure, can be obtained electronically The microtransducers are connected to an amplifier (Vingmed Unit UP 10B) The three outputs are then written out on a three channel recorder (MFE-recorder) Each channel on the paper record is 50 mm wide On the first channel the urethral pressure profile is recorded, on the second channel, the total bladder pressure, and on the third channel, the differential pressure between urethra and bladder The frequency range of the recorder is 0 - 80 Hertz The recording speed of the paper was 5 0 mm/sec The withdrawal speed of the recording catheter was 2 5 mm/sec

Specifications of the pressure transducer (model PC 771) are (figure 4 1)

type of sensor	silicon strain gauge
pressure range	−300 to +400 mm Hg
active measuring surface	0 75 mm^2
sensitivity	1 2 to 5 0 mV/V/100 mm Hg
temperature error band	3 cm H_2O from 23 – 38°C
drift	less than 1 5 cm H_2O per hour
linearity and hysteresis (combined)	within ± 0,5% BSL, of selected range (e g ± 0,5 mm Hg for a range of 0 to 100 mm Hg)
volume displacement	1 x 10 mm^3/136 cm H_2O
frequency response	0 - 20 kHz
electrical leakage	less than 2 5 micro amp at 500 Vdc
length of the catheter	20 cm

4 2 2 CALIBRATION PROCEDURE

The transducers are calibrated in a specially designed catheter manometer calibration unit (Asmussen et al , 1975) The catheter with the two micro transducers is placed in the fluid filled pressure chamber of the calibration unit (see figure 4 1) Through a 3-way cock the pressure chamber is con

nected to a fluid column for static calibration. On the upper side of the pressure chamber is a tubular opening closed during static calibration. Dynamic calibration can be carried out by placing a rubber balloon around the tubular opening and inflating the balloon with air to a desired pressure. When the balloon bursts, the pressure in the chamber instantly returns to atmosferic pressure. During the calibration procedure the pressure chamber can be filled with sterilizing liquid (diluted R-alkyl-dimethyl benzyl ammonium chloride). The unit thus serves as calibration unit and at the same time as sterilization unit (LINDSTROM AND ULMSTEN, 1978).

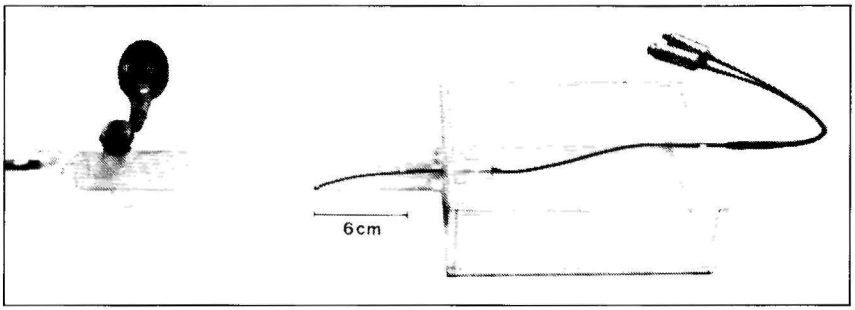


Figure 4.1. The microtransducer catheter placed within the pressure chamber of the catheter manometer calibration unit.

4.2.3. MEASURING TECHNIQUE

Simultaneous urethrocystometry, including measurement of the total bladder pressure and the urethral pressure profile, was performed by means of a dual channel microtransducer according to the technique described by Asmussen and Ulmsten (ASMUSSEN AND ULMSTEN, 1975). The functional urethral length (FUL), the anatomic urethral length (AUL), the distance from the internal meatus to the point of maximum urethral pressure (PMP), the total bladder pressure (TBP), the maximum urethral pressure (MUP), and the difference between these two, i.e., urethral closure pressure (UCP), were measured. These variables are defined according to the Standardization Committee of the International Continence Society (BATES et al., 1977). In addition, the area under the urethral closure pressure curve (integrated pressure-IP) was calculated by planimetry (Digiplan Typ. 8550). All pressure measurements are expressed in cm H_2O, and all length measurements in mm.

Before each recording session the catheter was sterilized and calibrated in the catheter manometer calibration unit (ASMUSSEN et al., 1975). Prior to the study session the subject was asked to empty her bladder. With the

subject in the lithotomy position, a no. 8 Fr. catheter was inserted into the bladder and residual urine, if any, was measured. The bladder was filled with 300 ml of normal saline at body temperature through the same catheter at a filling rate of 50 ml/min. The filling catheter was removed and the recording catheter that contained the two microtransducers was introduced and advanced into the bladder. The microtransducer catheter was fixed at ± 1 cm from the external meatus to the mobile steering arm of a motor driven instrument (Vingmed UP 20), which allows forward and reverse movement of the catheter through the urethra at a constant speed of 2.5 mm/sec. Since the urethral pressure profile may be influenced by the degree of bladder filling (TANAGHO et al., 1966; GRIFFITH, 1973; OBRINK et al., 1977) all recordings were made at a bladder volume of approximately 300 ml. Measurements were made in both the supine and sitting positions and care was taken that the microtransducers faced toward the lateral urethral wall (BANNINGER et al., 1980). Three consecutive profiles at rest and one profile under repeated cough provocation were recorded in each position at each study session in all subjects. The urethral pressure profile is influenced by the degree of relaxation of the subject. When several profiles are made from the same woman, the profile with the lowest urethral pressure is probably the most representative of the basal condition (PLANTE AND SUSSET, 1980; CONSTANTINOU AND GOVAN, 1980). Investigation of the short term variability of the urethral pressure profile demonstrated that the lowest pressures were generally reached in the third and/or fourth recordings (see results chapter 5). Other investigators have shown that repeated recordings of six or more profiles within the same study session are almost identical from the third one onward (OBRINK et al., 1977).

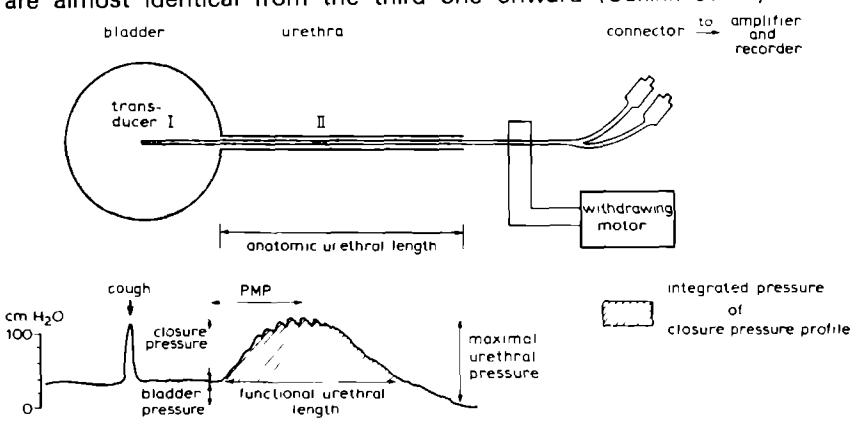


Figure 4.2 Schematic representation of urethral closure pressure profile showing definitions of the variables measured.

Therefore, in the studies relating to the long term reproducibility and the influences of low dose oral contraceptives, and in the studies described in the chapters 6 and 7, the measurements from each third urethral pressure profile at rest were the ones subjected to statistical analysis All recordings were obtained and interpreted by one investigator (v G)

4 3 HORMONE DETERMINATIONS

4 3 1 FOLLICLE-STIMULATING HORMONE (FSH), LUTEINIZING HORMONE (LH) AND PROLACTIN

Concentrations of LH, FSH and prolactin were measured by specific, homologous, double antibody solid-phase radioimmunoassays (DASP, Organon Teknika bv , Oss, The Netherlands) Prolactin was measured with a reagent set (VLS no 4) provided by the National Institutes of Health (Bethesda, Maryland, USA) LH and FSH were assayed with the use of rabbit antisera against highly purified human chorionic gonadotropin (hCG) and FSH preparations, respectively Within the range of the standard dose-response line for LH (2 to 400 mIU First International Reference Preparation (IRP) of human pituitary LH (MRC 68/40) for immunoassay per milliliter of serum), the most highly purified FSH (6000 IU/mg) and thyroid stimulating hormone (TSH) (4 IU/mg) preparations currently available showed some apparent cross reaction, for which the LH contamination of these preparations was responsible The antiserum against FSH failed to show any significant cross-reaction with the IRP's for LH, hCG, TSH and their subunits within the range of the standard dose response line for the FSH system (1 to 100 mIU First IRP of human pituitary gonadotropins LH and FSH for bioassay (MCR 69/104) per milliliter of serum) after absorption of the FSH antiserum with purified hCG (Hunter and Bennie, 1971) Radiolabelling with ^{125}I (The Radiochemical Centre, Amersham, United Kingdom) was applied to pure human LH (hLH NM14, immunopotency 6440 IU/mg) and FSH (IRE, Fleurus Belgium, immunopotency 6000 IU/mg) preparations for use in the respective assays (Greenwood et al , 1963) After iodination, purification was achieved by gel filtrations on Sephadex G-25 and Sephadex G 100 (Pharmacia Fine Chemicals AB, Uppsala, Sweden) The lower detection limits were fixed at $B/B_o = 0\,9$ and revealed 2 mIU/ml for the LH-assay, 0 7 mIU/ml for the FSH-assay, and 1 ng/ml for the prolactin assay The intra assay and inter-assay variabilities for means of duplicate measurements were calculated from several pools of serum (Rodbard, 1974) and were respectively 8 6% and 16 3% for LH, 8 1% and 15 5% for FSH, 6 3% and 14 6% for prolactin

4 3 2 17β-ESTRADOL (E_2)

Serum concentrations of E_2 were measured by specific, DCC radioimmunoassay (THOMAS et al 1977) Rabbit antiserum was raised against E_2-6-(o carboxymethyl)-oxime-BSA Within the range of the standard dose-response line (3 to 400 pg, i e , 0 01 to 1 47 pmol E_2 standard per tube), a variety of relevant, related steroids showed cross reactivities of less than 1% at 50% inhibition Radiochemical purity of tritiated steroid (2,4,6,7-^{3}H E_2, The Radiochemical Centre, Amersham, U K ; specific activity 112 Ci/mmol) was checked by chromatography on Sephadex LH-20 columns The recovery of tritiated E_2 added to serum was 91 $\pm$ 7 (SD)% (n $-$ 36) following extraction with diethyl ether Method blanks were always much lower than the minimum detectable dose (4 pg E_2 per assay tube at $B/B_0 = 0\ 9$) and were, therefore, neglected The intra-assay and inter-assay variabilities as calculated from several pools of serum (cf description of LH assay) were 5 5% and 14% respectively

4 3 3 PROGESTERONE (P)

Serum concentrations of P were measured by specific, DCC radioimmunoassay (THOMAS et al , 1977) The rabbit antiserum used was raised against 11 alpha-OH-progesterone-hemisuccinate-BSA Within the range of the standard dose-response line (8 to 1000 pg, equivalent to 0 03 to 3 18 pmol P standard per tube), all the relevant, related steroids showed cross-reactions of less than 0.1% at $B/B_0 = 0\ 5$ Radiochemical purity of the tritiated P used (1,2,6,7-^{3}H P, The Radiochemical Centre, Amersham, U K , specific activity 100 Ci/mmol) was checked by chromatography on Sephadex IH-20 columns. The recovery of tritiated P added to serum samples was 97 $\pm$ 3 (SD)% (n = 37) following extraction with diethyl ether Method blanks were always much lower than the minimum detect able dose (10 pg P standard per assay tube at $B/B_0 = 0\ 9$) and were, therefore, neglected The intra assay and inter-assay variabilities as calculated from several pools of serum (cf description of LH assay) were 7 2% and 11% respectively

4 3 4 17α OH PROGESTERONE (17 OH P)

Plasma 17-OH P levels were measured by RIA using an antiserum raised in sheep against 11 desoxycortisol-21-hemisuccinate conjugated to bovine serum albumin This antiserum cross-reacts 100% with both 17-OH P and 11 desoxycortisol The lower limit of detection of the assay was 5 ng/100 ml and the mean intra-assay coefficient of variation was 6 1% at a 17-OH-P level of 82 ng/100 ml (n = 8) (SMALS et al , 1978)

The female urethral pressure profile (UPP)

Reproducibility, axial variation and effects of low dose oral contraceptives

5.1. INTRODUCTION

The variability of the urethral pressure profile as recorded with microtransducer catheters was investigated in a group of healthy nulliparous women in both the supine and sitting positions, according to a standardized methodology under similar physiological conditions The aims of the present study were to investigate

a the short term reproducibility, i e , the variability between serial urethral pressure profile recordings during the same study session,
b whether there are systematic changes in the urethral pressure profile measurements when a series of successive recordings is made and, if so, which of these profiles is most representative of the basal condition,
c the long term reproducibility, i e , the variability between urethral pressure profile recordings obtained from successive study sessions one week apart,
d the effect on urethral pressure profile measurements of rotational variations in the orientation of the transducer membrane with respect to the urethral wall, and
e effects of postural changes on the urethral pressure profile and dynamic effects

Included in the study design was also an evaluation of the influence of low dose oral contraceptives on the urethral pressure profile
Throughout the paper the letters a) to e) will be used to refer to the aims listed above

5.2. SUBJECTS AND METHODS

Thirty-two healthy nulliparous women, age 18 - 35, who used low dose oral contraceptives, agreed to participate in this study

5 2 1 SHORT TERM REPRODUCIBILITY

The assessment of the short term reproducibility of the urethral pressure profile measurements and the investigation as to which of several serially recorded profiles can be considered the most representative of the basal condition (aims a and b) were carried out in 12 subjects (group I) (mean age 22,4 $\pm$ 3,8) In these 12 subjects 5 successive urethral pressure profile recordings at rest in the supine position and 3 successive recordings at rest in the sitting position were performed with the membrane of the micro transducer oriented laterally

5 2 2 LONG TERM REPRODUCIBILITY AND ANALYSIS OF ROTATIONAL VARIATIONS

Long term reproducibility and analysis of rotational variations (aims c and d) were studied in another 20 women (group II) (mean age 23,3 $\pm$ 4,3) who were on low dose oral contraceptives (OC) (150 mcg levonorgestrel and 30 mcg ethinyl estradiol per tablet, Microgynon 30®) The differences between periods of OC-use and the OC-free periods with regard to the urethral pressure profile measurements were evaluated Three study sesions at approximately one week intervals were performed The first study session was timed on the fifth or sixth day after the last OC pill and the two other study sessions were performed at one week intervals during the following pill cycle Prior to each study session blood samples were taken for determination of LH, FSH, E_2 and P as previously described (chapter 4 3) At each study session five serial profiles at rest, in both the supine and sitting positions, were recorded The first three profiles were recorded with the membrane of the transducer directed laterally, the fourth profile, with the transducer directed ventrally, and in the fifth profile the transducer membrane was directed dorsally The urethral pressure profile variables measured from each third, fourth and fifth profile were used in the statistical comparisons In addition, one urethral pressure profile during dynamic testing, i e coughing and/or squeezing, was performed in both positions

A summary of the urethral pressure profile recordings performed in the 20 women with regard to the position of the transducer membrane and the times during the pill cycle is given in Table 5 1 In a few subjects measurements with the transducer membrane in the ventral and/or dorsal positions were not performed for various reasons

TABLE 5.1. Summary of the UPP recordings in group II.

Time	lateral	ventral	dorsal	Number of women
OC free	x	x	x	
OC I	x	x	x	N = 10
OC II	x	x	x	
OC free	x			
OC I	x	x	x	N = 2
OC II	x	x	x	
OC free	x	x		
OC I	x	x		N = 5
OC II	x	x		
OC free	x			
OC I	x	x		N = 3
OC II	x	x		

5.3. STATISTICAL ANALYSIS

5.3.1. GROUP I (N = 12)

a) The variance of the first three measurements of each urethral pressure profile variable was calculated separately for each subject. The square root of the mean variance over the 12 subjects and the corresponding coefficient of variation were considered to be a measure of the short term reproducibility. To allow proper comparison with respect to reproducibility between length and pressure variables, and between recordings in the supine and in the sitting positions, the coefficient of variation, which is the standard deviation expressed as a percentage of the mean value, i.e., CV = SD/mean x 100%, was also calculated. The variables of the first three profiles in the supine and in the sitting positions were used to allow for comparison with literature.

b) The means and the standard deviations (SD) for each urethral pressure profile variable for the 12 women were calculated according to the serial number of the measurements within the same study session.

5 3 2 GROUP II (N = 20)

c) The influence of low dose oral contraceptives on the urethral pressure profile measurements was statistically tested separately for each transducer direction by the Scheffe method for simultaneous contrast testing (SCHEFFÉ, 1959) Since no influence of low dose oral contraceptives on the urethral pressure profile measurements could be demonstrated (see results below), the recordings from these three study sessions were regarded as long term replicates The mean values and the standard deviations of the urethral pressure profile variables of each third profile measured with the transducer membrane oriented laterally, were calculated for each subject over these three study sessions in both the supine and sitting positions Long term reproducibility was mea sured by the square root of the mean variance and by the mean value of the coefficients of variation over all 20 women

d) For the 12 women who had urethral pressure profile recordings performed with the transducer membrane in the ventral, lateral and dorsal positions (see Table 5 1) the differences between these three positions were evaluated by a two-way analysis of variance (subject x transducer position, general model, fixed effects) followed by a contrast analysis according to SCHEFFE (1959) Moreover, the differences between the lateral and ventral positions were tested by a two-way analysis of variance including all 20 subjects

5.4. RESULTS

5 4 1 SHORT TERM REPRODUCIBILITY (A)

The short term reproducibility of the individual urethral pressure profile variables, as measured by the square root of the mean intrasubject variance and the corresponding coefficient of variation, is shown in Table 5 2 It can be seen from this table that urethral pressure measurements show a greater variability than urethral length measurements Except for the distance from the internal meatus to the point of maximum pressure (PMP), the reproducibility is about the same for recordings in the supine and sitting positions

TABLE 5 2 Short term reproducibility Mean, standard deviations (SD) and coeffi cients of variation (CV) of urethral pressure profile (UPP) variables in successive recordings within the same study session (N – 12)

	SUPINE			SITTING		
UPP variable	mean	SD	CV%	mean	SD	CV%
FUL (mm)	33 5	1 9	5 7	40 3	2 1	5 1
AUL (mm)	41 2	1 5	3 6	47 0	2 1	4 4
PMP (mm)	16 7	1 6	9 6	21 2	3 3	15 4
TBP (cm H_2O)	14 1	0 05	0 4	31 1	0 3	1 1
MUP (cm H_2O)	96	6 7	6 9	135	8 3	6 2
UCP (cm H_2O)	82	6 5	7 9	104	8 4	8 2
IP/10	72	6 0	8 3	122	8 6	7 1

5 4 2 SERIAL MEASUREMENTS (B)

The mean values and the standard deviations of the urethral pressure profile variables measured in the supine position according to the serial number are shown in Table 5 3. In these serial determinations, the length measurements tended to be more stable than the pressure measurements. The mean values of the pressure variables decreased from the first registration to the fourth registration In 10 of the 12 women the lowest values of the pressure variables were observed in the third and fourth registrations An increase in all urethral pressure profile variables was observed in the fifth registration. The total bladder pressure remained constant during the study session (mean value: 14 1 ± 3 0 cm H_2O.)

TABLE 5 3 Mean ± SD of urethral pressure profile (UPP) variables according to the serial number of the urethral pressure profile within the same study session

UPP variable	1	2	3	4	5
AUL (mm)	41 5 ± 5 1	41 4 ± 5 0	40 9 + 5 2	40 9 ± 5 3	41 5 ± 5 3
FUL (mm)	33 3 ± 5 1	33 9 ± 4 0	33 3 ± 4 6	33 1 ± 3 3	33 7 ± 3 9
PMP (mm)	16 5 + 4 0	16 7 ± 4 3	17 1 ± 3 8	17 0 ± 3 9	17 3 ± 4 1
MUP (cm H_2O)	100 3 ± 17 8	94 7 ± 16 6	93 5 ± 15 2	92 7 ± 13 6	97 8 ± 18 5
UCP (cm H_2O)	86 0 ± 17 8	80 7 ± 17 1	79 3 ± 15 7	78 5 ± 14 0	83 8 ± 18 8
IP/10	74 3 ± 18 4	73 5 ± 20 3	68 8 ± 20 1	67 8 ± 17 4	68 8 ± 18 4

5.4.3. EFFECTS OF LOW DOSE ORAL CONTRACEPTIVES

Mean values ± SD for serum hormone levels of LH, FSH, 17β-estradiol (E_2) and progesteron (P) for the three study times are given in Table 5.4. Study sessions were performed and blood samples were taken at least 8 hours after the daily OC intake.

TABLE 5 4 Mean ± SD for FSH, LH, E_2 and P at the three study times

	OC free	Pill I	Pill II
LH (mIU/ml)	15 ± 6	13 ± 7 6	12 ± 11
FSH (mIU/ml)	3 8 ± 1.8	2 7 ± 1.5	2 1 ± 1 4
E_2 (pg/ml)	53 ± 24	27 ± 10	22 ± 33
P (ng/ml)	1 0 ± 1.5	0.6 ± 0 2	0.6 ± 0 5

There were no significant differences between serum levels of gonadal steroids during the pill cycle. As could be expected, FSH and E_2 levels were significantly increased during the OC free period when compared with the levels during OC use ($p < 0.05$) (sign test).

Serum concentrations of ethinyl-estradiol, the synthetic estrogen used in the current formulations of OC, reach peak levels within half to two hours after ingestion and then rapidly decrease below the level of detection (i.e., 20 pg/ml) within 8 hours (Brenner et al., 1980). Crossreaction of ethinyl-estradiol with E_2 in the RIA is $< 0.3\%$, so there is no significant effect of ethinyl-estradiol on the levels of E_2 measured. After daily ingestion of 150 mcg levonorgestrel, serum concentrations of levonorgestrel remain at about the same level, i.e., approximately 1 ng/ml (Spona et al., 1980).

The Scheffé method for simultaneous contrast testing demonstrated no significant differences in urethral pressure profile measurements between the two times in the pill cycle. Also, there were no significant differences between the mean values of the urethral pressure profile variables obtained in the OC free period and the corresponding values averaged for the two recordings during the pill cycles (p-values ranging from 0.06 to 0.99 for different urethral pressure profile variables, measuring positions and transducer directions).

5.4.4. LONG TERM REPRODUCIBILITY (C)

The square roots of the mean variances and the mean coefficients of variation for each urethral pressure profile variable for the 20 healthy women,

studied at three successive occasions one week apart, are given in Table 5 5 It can be seen from this table that the length measurements are more reproducible in time than the pressure measurements Except for the distance from the internal meatus to the point of maximum pressure (PMP), the reproducibility is about the same for recordings made in the supine and sitting positions

TABLE 5 5 Long term reproducibility Means of the individual standard deviations (SD) and coefficients of variation (CV) of urethral pressure profile (UPP) variables recorded three times at one week intervals (N = 20)

	SUPINE			SITTING		
UPP variable	SD	CV	number with CV < 10%	SD	CV	number with CV < 10%
FUL (mm)	1 8	5 5%	16	2 0	5 0%	19
AUL (mm)	1 7	4 0	19	1 7	3 5	20
PMP (mm)	1 5	7 7	19	3 3	11 6	9
TBP (cm H_2O)	1 4	8 6	14	2 8	7 2	15
MUP (cm H_2O)	8 5	7 8	14	12 2	8 3	13
UCP (cm H_2O)	8 2	9 7	13	12 6	10 9	13
IP/10	10 2	13 5	9	14 6	14 7	7

5 4 5 ANALYSIS OF ROTATIONAL VARIATIONS (D)

The results of the urethral pressure profile recordings with the membrane of the transducer directed ventrally, laterally and dorsally are given in Table 5 6 The results of the analysis showed no evidence for significant differences beween urethral pressure profile measurements when the transducers were directed laterally or dorsally When the membrane of the transducer was oriented ventrally (i e toward the symphysis pubis), however, all urethral pressure measurements were significantly increased as compared with the measurements in the lateral and dorsal orientations The length variables measured with the transducer oriented ventrally were significantly shorter than those obtained with the other two orientations Thus, the ventral urethral pressure profile shows a higher and shorter pattern than the lateral and dorsal urethral pressure profile recordings

TABLE 5.6. Mean values of urethral pressure profile (UPP) variables, two way analysis of variance and contrast analysis with regard to the position of the catheter.

UPP	Mean values			Two-way analysis of variance		Contrast analysis according to Scheffé			
variables	lateral	ventral	dorsal	lat.-ventr. diff.	p values*	lat.-dors. diff.	p values	ventr.-dors. diff.	p values
SUPINE	N = 20	N = 20	N = 12	N = 20		N = 12		N = 12	
FUL (mm)	31.1	29.0	30.3	2.1	0.000	1.1	0.01	− 1.0	0.02
AUL (mm)	37.7	34.0	37.7	3.7	0.000	0.2	0.82	− 4.0	0.000
PMP (mm)	16.3	15.4	18.2	0.9	0.003	−0.7	0.23	− 1.8	0.03
MUP (cm H_2O)	91	100	85	− 8.6	0.000	−0.8	0.93	9.2	0.001
UCP (cm H_2O)	76	85	71	− 8.4	0.000	−0.6	0.96	8.1	0.001
IP/10	68	72	61	− 4.1	0.04	1.7	0.68	5.0	0.04
SITTING									
FUL (mm)	35.7	33.9	35.7	1.8	0.000	−0.2	0.93	− 2.1	0.000
AUL (mm)	43.1	42.1	43.6	1.0	0.004	−0.6	0.35	− 1.4	0.005
PMP (mm)	18.4	21.8	20.1	− 3.4	0.000	−0.4	0.84	1.5	0.06
MUP (cm H_2O)	119	137	111	−19	0.000	3.8	0.29	22	0.000
UCP (cm H_2O)	88	106	80	−18	0.000	4.1	0.27	22	0.000
IP/10	89	98	81	− 8.9	0.002	0.2	0.99	8.3	0.02

* P = 0.000 is $p < 0.001$

Both length and pressure measurements increased when the subject assumed the sitting position The relationship of the axial variations in intraurethral pressures described above was similar for the recordings in the supine and sitting positions In the sitting position, however, a change in pattern of the intraurethral pressure was often observed with a marked increase in urethral closure pressure in the distal part of the functional urethra, i e , in the zone where the urethra is attached to the pelvic floor This zone of increased pressure in the distal urethra was most pronounced when the transducer membrane was oriented ventrally As a result, most profiles recorded in the sitting position with the transducer facing ventrally showed in greater or lesser degree a double humped (camel-back) configuration, with one pressure maximum situated in the proximal third, i e , at about 1,5 cm from the bladder neck, and the second in the distal third of the functional urethra In the same subjects maximum urethral pressures at rest in the sitting position were measured in some profiles in the proximal third and in other profiles in the distal third of the functional urethra During dynamic testing, i e coughing and voluntary holding, an increase in urethral pressure response was observed in the distal part of the functional urethra in almost all subjects in both the supine and sitting positions (Figs 5 1 and 5 2) The amplitude of the increase in urethral closure pressure generally was greater when the transducer was in the ventral position as compared to the increases observed with the transducer in lateral and dorsal positions (Van Geelen et al , 1983)

5 5 DISCUSSION

There is no unanimity in the literature as to which urethral pressure profile at rest should be used when several profiles are recorded within the same study session Some investigators (Asmussen, 1975, Henriksson et al , 1979, Rud, 1980b) calculate the mean values from the first three successive profiles whereas others use the measurements from the third profile only (Obrink et al , 1977) The high degree of variability observed in successive urethral pressure profile measurements is probably due to activity of the striated musculature in the urethral wall and in pelvic floor (Plante and Susset, 1980) Therefore, when several profiles at rest are recorded within the same study session, the profile showing the lowest resting pressure probably is most representative of the basal condition, since this profile should be least influenced by voluntary muscle activity

From this study it appears that within a series the lowest profile is generally reached in the third or fourth recordings The small increase in urethral pressure profile values in the fifth profile in this study may have been a psychological effect since the subjects were aware from the previous explanation of the study protocol that the study session was nearly over The mean values of the urethral pressure profile variables for this age group averaged over the four cycle times are in agreement with those found by investigators using the same technique (Asmussen, 1975, Obrink et al , 1977, Rud, 1980b) and by other investigators using different techniques (Enhorning, 1961, Plante and Susset, 1980)

Variations in sex steroid levels affect the female urinary tract During the normal menstrual cycle increasing levels of estrogens lead to an increase in urethral length and to an increase in amplitude of the vascular pulsations in the urethral wall (Van Geelen et al , 1981; chapter 6) High doses of estrogens administered orally or intravaginally result in a significant increase in urethral length and in a better transmission of pressure over the urethra (Rud, 1980c, Hilton and Stanton, 1982c) Caine and Raz (1973) observed an increase in urethral closure pressure in stress incontinent women treated with estrogens whereas a number of women treated with a progesterone derivate showed a decrease in urethral closure pressure Rud (1980c) and Van Geelen et al (1981) observed no significant changes in urethral measurements attributable to progestagen treatment or to serum levels of progesterone in the human female.

After daily ingestion of low dose oral contraceptives, serum levels of synthetic steroids and of endogenous gonadal steroids are generally lower than the levels of E_2 and P observed during the menstrual cycle (see chapter 6) E_2 levels in the OC free period were approximately twice those measured during the pill cycle, whereas P levels were almost equal at the three study times No effects of low dose oral contraceptives on the variables of the urethral pressure profile were observed

It has been shown that oral contraceptives lead to an increase in urinary tract infection, and the increased incidence of urinary tract infections has been found to be related to the dosage of estrogen in the pill (Interim report R C G P , 1974) The mechanism underlying this relationship is not known The results of the present study provide no explanation for the increased incidence of urinary tract infections during oral contraceptives use

For proper assessment of the short term and long term reproducibility, serial measurements in healthy women at different times under similar and

standardized conditions are mandatory Since no influence of low dose oral contraceptives on the variables of the urethral pressure profile could be demonstrated, urethral pressure profiles performed at one week intervals under similar conditions may be considered as replicates and can be used for determination of the long term reproducibility of the urethral pres sure profile measurements

Except for the total bladder pressure the variability of the urethral pressure profile recordings with the membrane of the transducer in the lateral position is in the same range for both the measurements within the same study session (short term reproducibility) and for those at one week intervals (long term reproducibility) These findings are in agreement with those obtained by HILTON AND STANTON (1981), who with the same methodology observed no significant differences in variances of the urethral pressure profile variables due to time The reproducibility of the length measurements is similar in these two studies The variances of the pressure measurements in the present study are, however, approximately twice those obtained by HILTON AND STANTON (1981) It is unlikely that variation caused by random sampling is the only explanation for differences of this magnitude with the sample sizes involved in these two studies A possible explanation for the difference in the reproducibility of the urethral pressure measure ments is the fact that the present study was carried out in young healthy nulliparous women, whereas the study by HILTON AND STANTON (1981) was carried out in women with a variety of urinary symptoms Urethral pressure profile recordings in healthy nulliparous women generally show a relatively high urethral pressure and marked arterial pulsations in the urethral wall These specific features of the normal urethral pressure profile decrease with increasing age and after vaginal delivery, and are generally absent in women with urinary symptoms (e g , stress incontinence) (ENHORNING, 1961, RUD, 1980b SUSSET AND PLANTE, 1980, VAN GEELEN, et al , 1982, chapter 7) The greater variability of the pressure measurements observed in this study may be related to the higher baseline of urethral pressure values in normal subjects The variability of the UPP variables in this study population as expressed by the coefficients of variation is not as great as the variability reported when a water perfusion technique was used in a group of incontinent women (TOGURI et al , 1980)

Other investigators, using different recording catheters, also observed that the pattern of the urethral pressure profile is substantially influenced by the axial position of the catheter (GHONEIM et al , 1975, BANNINGER et al , 1980, HILTON AND STANTON, 1981, WARD AND HOSKER, 1982, MARTINEZ AND CONSTAN TINOU, 1982) Urethral pressure profile recordings with the membrane of

the transducer directed ventrally show shorter urethral length measurements and higher urethral pressures than recordings obtained with the transducer oriented laterally or dorsally The shorter urethral length measurements can be explained by the anatomy of the urethra, which bends ventrally around the symphysis so that the ventral wall is a bit shorter than the lateral and dorsal walls For the measurements in the supine position, maximum urethral pressures in the supine position were generally measured at the level of the midurethra proximal to the urogenital diaphragm (Westby and Asmussen, 1981) The higher maximum urethral pressure and urethral closure pressure measured at the ventral wall can be explained by the presence of of striated muscle fibers which are most concentrated in the ventral wall at midurethra and almost absent in the dorsal urethral wall The effects of axial rotation of the catheter on the urethral pressure profile recordings were similar for the measurements in the supine and in the sitting positions These results indicate an asymmetrical distribution of urethral closure forces in healthy women

Irrespective of the position of the catheter all urethral pressure profile values increased when the subject changed from the supine to the sitting position. For all catheter positions the maximum urethral pressure increased more than the total bladder pressure, resulting in an increased urethral closure pressure Similar observations in normal subjects regarding positional changes from supine to sitting or to standing position have been made by other investigators (Henriksson et al , 1977, Witherow and Tiptaft, 1978) The postural changes are not due to raised intra abdominal pressure, since the increase is not seen when the patient remains supine and the intra-abdominal pressure is raised by artificial means (George and Fenely, 1978) Moreover, if only hydrostatic pressure had induced the increase in pressure, the rise in total bladder pressure and maximum urethral pressure would have been of the same magnitude, and no change in urethral closure pressure would have been observed Actually, the increase in maximum urethral pressure was about twice the increase in total bladder pressure Consequently, the increase in total bladder pressure was paralleled by an increase in urethral closure pressure of almost the same magnitude The positional changes in urethral pressure profile must be explained by the increased pressure in the lower part of the abdomen exerted by the abdominal viscera and by the increased activity of the striated muscles of the pelvic floor which lengthen the urethra and compress the distal urethral segment The increase in urethral closure pressure in the sitting position was most obvious in the distal third of the functional urethra, i e , in the zone where the striated muscles of the pelvic

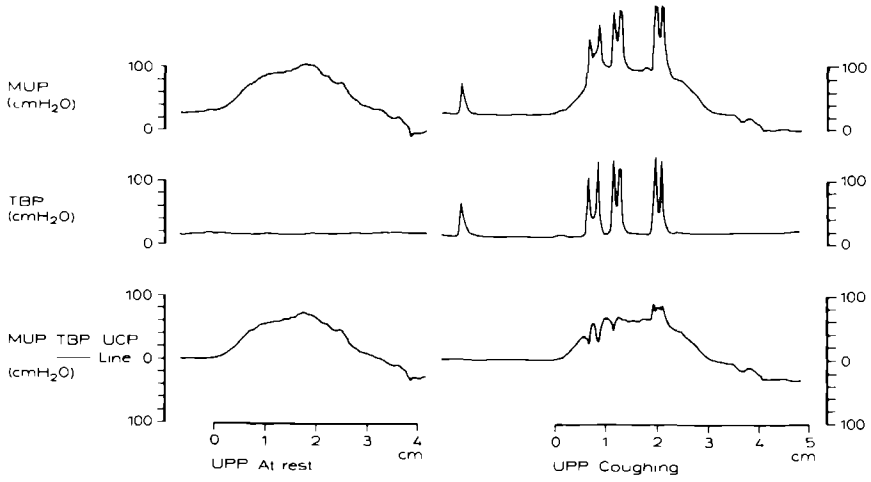


Figure 5 1 UPP recording in the supine position Transducer oriented laterally The upper tracing is the MUP, the middle tracing is the TBP, and the lower tracing is the differential pressure, i e , UCP A static UPP at rest is shown on the left side of the figure, and a dynamic UPP during coughing is shown on the right Coughing induces an increase in urethral closure pressure at the level of midurethra

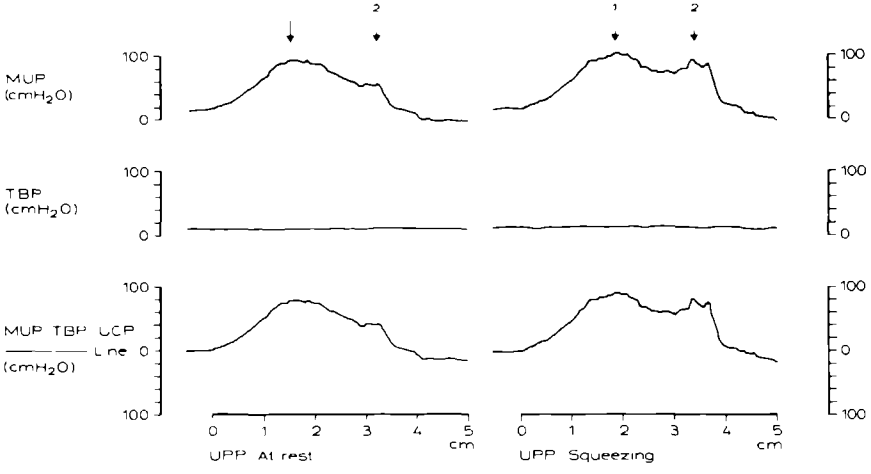


Figure 5 2 UPP recording in the supine position Transducer oriented laterally A static UPP at rest is shown on the left side of the figure and a dynamic UPP during squeezing is shown on the right Arrow 1 indicates point of maximum pressure at midurethra Arrow 2 indicates the level of attachment of the pelvic floor During squeezing, the dissociation between midurethra(1) and the distal segment of the functional urethra (2) where the striated muscles of the pelvic floor exert their effects, is apparent

floor exert their effect. The magnitude of the increase in urethral closure pressure was also influenced by the axial orientation of the transducer membrane, the greatest increase generally being observed with the transducer in the ventral position. The postural changes observed with different positions of the transducer membrane as well as observations made during dynamic testing, i.e., during coughing (figure 5.1.) and during voluntary contraction (figure 5.2.), support the concept of a two component sphincter mechanism in the female urethra (THUROFF et al., 1982). The proximal component consists of the bladder neck and proximal urethra which are situated above the urogenital diaphragm. The distal component is in the distal third of the functional urethra at the level where the urethra is attached to the pelvic floor.

5.6. SUMMARY

When serial urethral pressure profiles are recorded within the same study session under similar conditions lowest values for urethral pressure measurements are generally reached in the third or fourth recordings. The short term and long term reproducibility are generally the same for the measurements in the supine and in the sitting positions.
Orientation of the recording catheter and position of the study subject considerably influence the urethral pressure profile. Urethral pressure profile recordings with the transducer membrane oriented ventrally generally show a shorter urethral length and a higher closure pressure than those in which the pressure transducer is oriented laterally or dorsally. These observations indicate an asymmetrical distribution of urethral closure forces in healthy nulliparous women. All variables of the urethral pressure profile generally increase when the subject assumes the sitting position. The increase in urethral closure pressure is most prominent in the distal segment of the functional urethra and most probably results from increased activity of the striated muscles in urethral wall and in the pelvic floor.
There is no evidence that low dose oral contraceptives influence the variables of the urethral pressure profile.
It may be concluded that for proper comparison of the results of different urethral pressure profile studies, complete and precise description of the recording equipment and of the methodology employed is mandatory.

Urodynamic studies in the normal menstrual cycle

The relationship between hormonal changes during the menstrual cycle and the urethral pressure profile

6.1. INTRODUCTION

All of the various factors that contribute to the maintenance of a positive pressure gradient over almost the entire length of the urethra in normal women are not yet clarified Because of the closely related embryologic origin of the lower genital and urinary tracts, alterations in gonadal and/or gonadotropic hormones may influence the dynamic interaction between bladder and urethra Observations of differences in the urethral pressure profile between premenopausal and postmenopausal women (ASMUSSEN, 1975, OBRINK et al , 1977, SUSSET AND PLANTE, 1980) and of estrogen induced changes in the urethral pressure profile after the menopause (CAINE AND RAZ, 1973, FABER AND HEIDENREICH, 1977, RUD, 1980c) support the concept that steroid hormones, especially estrogens, may affect urethral physiology The aims of the present study were to investigate

a) whether the urethral pressure profile changes during the normal menstrual cycle,
b) whether such changes, if observed, are correlated with variations in blood levels of 17β estradiol (E_2), progesterone (P), E_2/P ratio and/or gonadotropic hormones, and
c) whether the urethral pressure profile variables are correlated with the height or weight of the woman

In addition the reproducibility of the urethral pressure profile measure ments with the methodology employed was evaluated

6 2. SUBJECTS AND METHODS

6 2 1 SUBJECTS

Thirty-six healthy nulliparous women, age 19 - 35, with a history of normal menstrual cycles, originally participated in this study After completion of the study, the criteria for a normal ovulatory cycle, described below, were met in 27 women In each subject urethral pressure profiles were recorded

serially at four times during one menstrual cycle according to the technique described in chapter 4. These times were early follicular phase (10 to 6 days before the presumtive ovulation day), midcycle (within ± 2 days of ovulation), early luteal phase (5 to 7 days after the rise in basal body temperature (BBT)) and late luteal phase (10 to 12 days after the rise in BBT)). The basic data of these 27 women are shown in Table 6.1.

TABLE 6.1. Basic data of the 27 nulliparous women in this investigation.

Variable		Range	Mean ± SD
Age	(yr)	19 - 35	25.4 ± 5.3
Menstrual cycle	(days)	27 - 36	29.6 ± 2.1
Weight	(kg)	45 - 80	60.4 ± 9.4
Height	(cm)	153 - 179	167.0 ± 6.0

Immediately prior to the profile measurements, samples of blood were taken for determination of serum levels of follicle stimulating hormone (FSH), luteinizing hormone (LH), prolactin, E_2 and P, as described in chapter 4.

6.2.2. HORMONAL CHANGES DURING THE NORMAL MENSTRUAL CYCLE

The menstrual cycle is divided into three phases: the follicular phase, the ovulatory phase and the luteal phase.

Follicular phase: in the early follicular phase of a normal menstrual cycle serum levels of estrogens are at a baseline level of approximately 30 to 50 pg/ml. Progesterone levels remain at a constant low level (< 0,5 ng/ml). Under influence of FSH, circulating levels of estrogens begin to increase 7 to 5 days before the LH surge, representing the maturation of the graafian follicle that will ultimately ovulate. Peak levels of estrogens are generally reached 48 to 24 hours before the LH peak and range from approximately 150 to 390 pg/ml. Estradiol (E_2) is the most potent natural estrogen, and its concentration during the menstrual cycle is 3 to 4 times higer than that of estrone.

Ovulatory phase: following the preovulatory peak of estrogens, serum E_2 levels decrease, whereas LH levels rapidly increase to reach midcycle LH peak within 48 hours. Coincident with the increase in LH, peripheral levels of P start to increase. After the LH peak, ovulation generally occurs within 6 to 36 hours and serum levels of E_2 rapidly fall to 50 to 160 pg/ml but usually start to increase again a few days after ovulation.

Luteal phase: during the luteal phase levels of E_2 and P both increase with

the maturation of the corpus luteum and reach their maximum concentrations 5 to 10 days after the LH peak Peak levels of P may vary from 6 to 25 ng/ml and E_2 levels range from 70 to 240 pg/ml Three or four days preceding menstruation, regression of the corpus luteum starts and E_2 and P levels decrease to baseline levels reached on about the third day of the cycle (BRIET, 1978, ERMINI, M AND CARENZA, L , 1980)

In this study, a cycle length from 24 to 36 days (TRELOAR et al 1967), a biphasic basal body chart and a progesterone level of 5 ng/ml or more on at least one occasion in the second half of the cycle (BRIET, 1978) were accepted as evidence for a normal menstrual cycle

Of the 36 subjects, 9 women with histories of normal menstrual cycles did not meet the criteria of a normal ovulatory cycle outlined above in 4 subjects ovulation could not be confirmed, in 2 subjects progesterone levels in the luteal phase were below 5 ng/ml and in another 2 subjects cycle lengths exceeded 36 days One subject failed to attend properly

Therefore, the data of 27 subjects are used to study the relationships beween hormonal changes during the menstrual cycle and changes in the *urethral pressure profile*

6 3 RESULTS

6 3 1 URETHRAL PRESSURE PROFILE VARIABLES DURING THE MENSTRUAL CYCLE

Values for the urodynamic variables averaged over the four cycle times in the group of healthy nulliparous women are shown in Table 6 2 As could be expected the mean values for all the variables studied were greater when the women were in the sitting position than in the supine position (See chapter 5)

TABLE 6 2 Mean ± SD of urethral pressure profile (UPP) variables in a group of 27 healthy nulliparous women

UPP variables	Supine	Sitting	N*
FUL (mm)	31 9 ± 4 9	38 2 ± 4 7	25
AUL (mm)	38 4 ± 4 7	44 9 ± 4 2	27
TBP (cm H_2O)	13 ± 3	31 + 5	27
MUP (cm H_2O)	98 ± 17	130 + 24	26
UCP (cm H_2O)	84 ± 18	98 + 23	22
IP/10**	70 ± 17	103 ± 32	26

N* – number of women for whom the sitting measurements were larger (averaged over the four cycle times) than the supine measurements

** – IP/10 is the integrated urethral closure pressure divided by 10

BBT charts and serum hormone levels confirmed the ovulatory nature of each menstrual cycle studied The mean values for the urethral pressure profile variables measured at the four times during the menstrual cycle together with the corresponding mean values for FSH, LH, prolactin, E_2 and P are given in Table 6 3

Changes were found in both functional urethral length and anatomic urethral length, and these changes were observed in both the supine and sitting positions Functional urethral length and anatomic urethral length were longer at midcycle and early in the luteal phase than at the beginning and end of the cycle (Table 6 3 , Fig 6 1)

TABLE 6 3 Mean ± SD for hormonal and urethral measurements in the group of 27 nulliparous women at four times in the menstrual cycle

	Follicular	Mid cycle	Early luteal	Late luteal
Hormonal				
E_2	59 0 ± 28 0	152 0 ± 99 0	160 0 ± 98 0	121 0 ± 71 0
P (ng/ml)	0 1 ± 0 1	1 5 ± 2 4	11 0 ± 8 0	8 0 ± 8 0
Prolactin (ng/ml)	7 4 + 5 2	5 8 ± 4 0	12 4 ± 11 5	9 9 + 6 0
LH (mIU/ml	13 2 ± 6 9	18 8 ± 13 6	17 2 ± 9 7	11 4 ± 6 7
FSH (mIU/ml)	3 3 ± 1 4	3 0 ± 1 8	2 5 ± 1 8	2 1 + 1 8
Urethral supine				
FUL (mm)	30 7 ± 5 1	33 3 ± 6 0	32 5 ± 5 5	31 0 ± 4 8
AUL (mm)	37 5 ± 4 6	39 7 ± 5 4	38 8 ± 4 9	37 5 ± 5 0
TBP (cm H_2O)	13 ± 3	13 ± 3	13 ± 4	13 ± 3
MUP (cm H_2O)	98 ± 20	102 ± 22	98 ± 19	96 + 20
UCP (cm H_2O)	83 ± 19	85 ± 19	84 ± 20	82 ± 20
IP/10	67 + 19	74 ± 20	71 ± 18	67 ± 19
Urethral sitting				
FUL (mm)	37 1 ± 5 3	38 8 ± 5 4	39 3 ± 5 4	37 7 ± 5 7
AUL (mm)	44 0 + 4 1	45 1 ± 5 0	45 9 ± 5 3	44 5 ± 4 9
TBP (cm H_2O)	31 ± 6	31 ± 5	32 ± 6	31 ± 6
MUP (cm H_2O)	131 + 24	131 ± 27	131 ± 28	127 ± 27
UCP (cm H_2O)	99 ± 22	100 ± 26	99 ± 27	95 ± 25
IP/10	101 ± 34	107 ± 36	105 ± 35	101 ± 34

In the calculations of the means and standard deviations for the hormonal variables the lower detection limit of the radioimmunoassay was used if an individual measurement was below this threshold

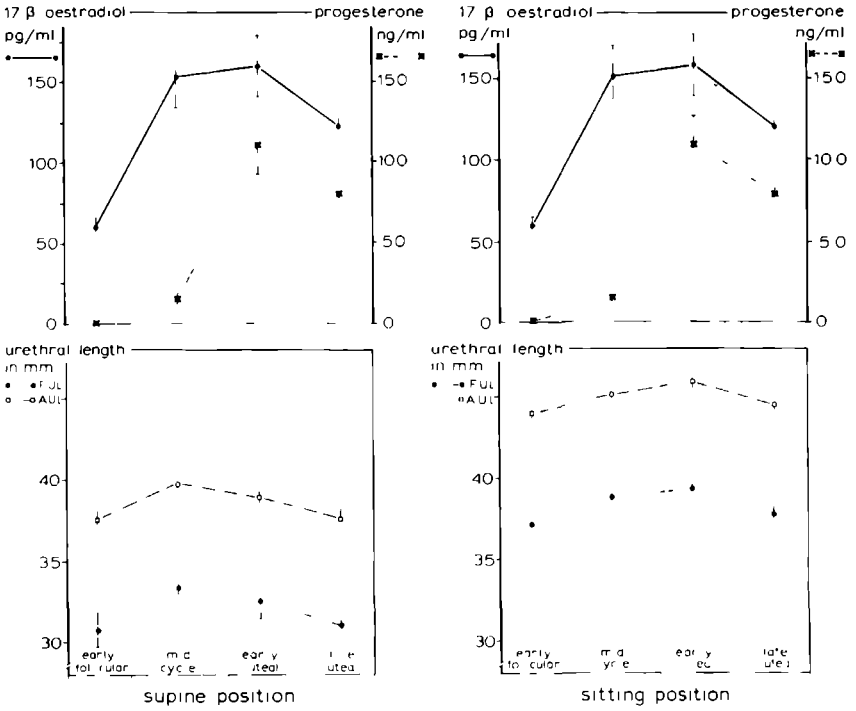


Figure 6 1 Serum levels of E_2 and P, measured at four cycle times and the corresponding values for FUL and AUL recorded at the same time Values are mean ± SEM

The midcycle and early luteal measurements did not differ significantly from one another. The mean increase in urethral length was small, approximately 2 mm or about 6% of the early follicular phase value. This lengthening, however, was observed in 22 of the 27 subjects, whereas s shortening was found in only one woman. Thus, both functional urethral length and anatomic urethral length were consistently increased during the times of the menstrual cycle when the E_2 levels were highest (Fig. 6.1.)
Averaging individual Kendall rank correlation coefficients revealed that functional urethral length and anatomic urethral length in the supine and in the sitting positions were significantly correlated with the serum concentrations of E_2 (Table 6.4.) There was no significant correlation between urethral length and P levels or the E_2/P ratios.

TABLE 6 4 Means of the 27 individual Kendall rank correlation coefficients for FUL and AUL versus levels of gonadal steroids in nulliparous women.

	FUL		AUL	
	Supine	Sitting	Supine	Sitting
E_2	0 34*	0 23*	0.30*	0 30*
P	0 11	0 12	0 08	0 22
E_2/P-ratio	0 06	0 09	0 05	0 16

* = significance level $P \leq 0\ 05$

Only small and insignificant alterations were observed in the mean intraurethral and intravesical pressure during the menstrual cycle. As a consequence, no significant correlations were found between maximum urethral pressure, total bladder pressure, urethral closure pressure and serum levels of E_2, P and E_2/P ratios (Fig. 6.2. and Fig. 6.3.).

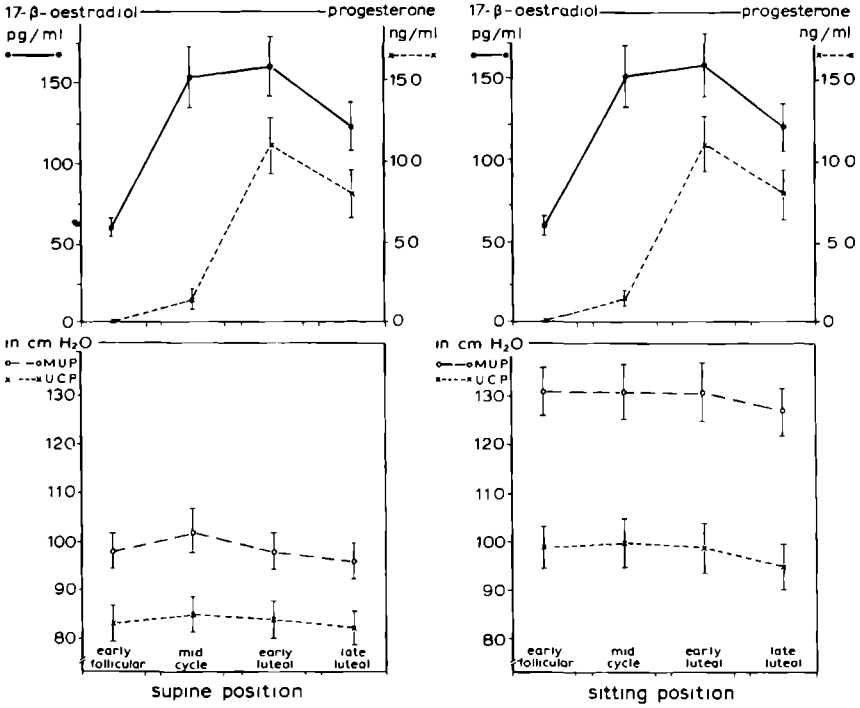


Figure 6 2 Serum levels of E_2 and P, measured at four cycle times, and the corresponding values for MUP and UCP recorded at the same time Values are mean ± SEM

The integrated pressure showed a tendency to increase with increasing E_2 levels (Fig 6 3) Since the integrated pressure is the resultant of functional urethral length and urethral closure pressure, this result was in agreement with the observed changes in urethral length

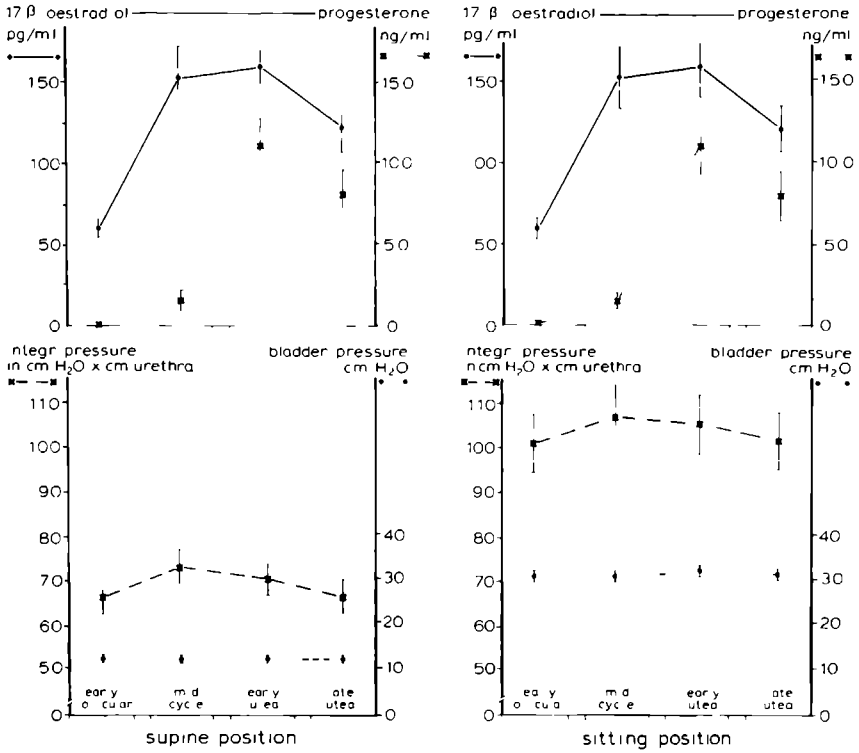


Figure 6 3 Serum levels of E_2 and P measured at four cycle times and the corresponding values for TBP and IP/10 recorded at the same time Values are mean ± SEM

In the urethral pressure profile recordings one frequently sees deflections superimposed on the intraurethral pressure recording which are synchronous with the arterial pulse The amplitude of the transmitted pulsations increased with increasing estradiol levels in 19 of the 27 subjects studied There was no marked change in the amplitude of the pulsations in seven subjects, and in only one woman did the pulsations decrease in the recordings when the levels of estradiol were elevated In the subjects who showed increased pulsations, the amplitude of the increase ranged from

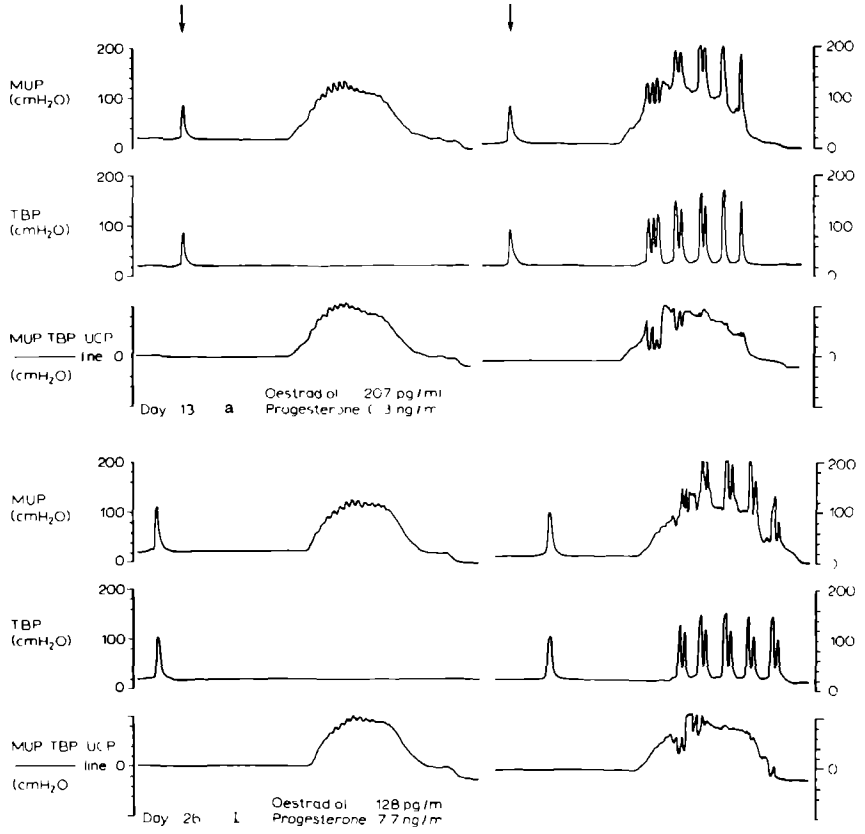


Figure 6.4 Urethral pressure profile recordings on day 13 (a) and on day 26 (b) of the menstrual cycle in the same subject. In each figure the upper tracing is the urethral pressure profile (MUP), the middle tracing, the total bladder pressure (TBP), and the lower tracing is the differential pressure, the urethral closure pressure (UCP). A static urethral pressure profile at rest is shown on the left side of each figure, and a dynamic urethral pressure profile during coughing is shown on the right. At the beginning of each recording both microtransducers are located in the bladder. Coughing (arrows) causes an equal pressure response by both microtransducers. The catheter is withdrawn through the urethra at 2.5 mm/sec. The proximal transducer measures the pressure exerted by the urethral wall on the transducer membrane, and the distal transducer at the tip records the intravesical pressure. Notice the difference between the transmitted arterial pulsations in the static urethral pressure profile on days 13 and 26 and compare with the corresponding E_2 levels

2 to 6 cm H_2O. The variations in the amplitude of the arterial pulsations, however, did not significantly influence the urethral pressure variables. Except for a small increase in urethral length variables, observed at mid-cycle and early luteal phase, the urethral pressure profile showed a consistent pattern over the four cycle times and no significant alterations were found in the pressure variables. Fig. 6.4. represents an example of static and dynamic urethral pressure profiles at two different times during one menstrual cycle.

6.3.2. URETHRAL PRESSURE PROFILE VARIABLES VERSUS HEIGHT AND WEIGHT

A possible relationship between the urethral pressure profile variables and the height and weight of the subjects was investigated. With use of the Kendall test for rank correlation, the averaged cycle value of anatomic urethral length appeared to be positively correlated with the body weight, but no other significant correlations were observed (Table 6.5.).

TABLE 6.5. Kendall rank correlation coefficient for the averaged cycle value of FUL and AUL versus weight and height in nulliparous women

	FUL		AUL	
	Supine	Sitting	Supine	Sitting
Weight	0.12	0 14	0.26**	0 32*
Height	0 07	0.02	0 13	0 18

* = significance level $p \leq 0\ 05$
** = significance level $p \leq 0.10$

6.4. REPRODUCIBILITY

Analysis of all the urodynamic data by means of a slippage test (Doorn bos, 1959) for each of the urethral pressure profile variables gave no indication of outlying observations.

Long term reproducibility of the urethral pressure profile variables recorded at 4 separate times during one menstrual cycle was evaluated from the means of the standard deviations and coefficients of variation for each urethral pressure profile variable for all 27 women following the same procedure as described in chapter 5 (Table 6.6.). The coefficients of variation varied considerably both between subjects with regard to the same variable and between variables in the same subject. From the data in Table

6.6., one can conclude that the reproducibility of the urethral pressure profile variables is about the same for the measurements in the supine and the sitting positions. Measurements of length are more reproducible than measurements of pressure, as also can be derived from the figures in the third and sixth column of Table 6.6., where is given for each variable the number of subjects that shows a coefficient of variation less than 10 percent.

The coefficients of variation of urethral length measurements in this study are slightly higher than the ones obtained during the pill cycle. The coefficients of variation of the pressure measurements are almost similar in both studies. It seems reasonable to conclude that the greater variability of the length measurements, observed in this study, can be accounted for on the changing levels of circulating estrogens during the menstrual cycle.

TABLE 6.6. *Mean of the individual standard deviations (SD) and coefficients of variations (CV) for the urethral pressure profile (UPP) variables in 27 nulliparous women.*

UPP	SUPINE			SITTING		
Variables	SD	CV (%)	No. of women with CV < 10%	SD	CV (%)	No. of women with CV < 10%
FUL (mm)	2.4	7.5	22	2.8	7.4	22
AUL (mm)	2.0	5.1	26	2.3	5.2	25
TBP (cm H_2O)	1.5	11.3	13	2.1	6.9	24
MUP (cm H_2O)	9.0	9.6	19	11.0	8.7	20
UCP (cm H_2O)	7.4	9.0	17	10.7	11.4	15
IP/10	7.8	11.6	14	13.7	14.1	13

6.5. DISCUSSION

The aim of the present study was to investigate the relationship between hormonal changes during the normal menstrual cycle and alterations in the urethral pressure profile. The influence of estrogens and progesterone on the lower urinary tract has been described in several studies (JEFFCOATE, 1965; CAINE AND RAZ, 1973; FABER AND HEIDENREICH, 1977; RUD, 1980c). In postmenopausal women, treatment with estrogen enhances proliferation

and maturation of the atrophic epithelium of the urethra and bladder trigone (Smith, 1977; Walter et al , 1978) Moreover, in postmenopausal women with genital prolaps and incontinence, treatment with estrogens has proved to be effective in improving the symtoms of stress incontinence and sometimes even restoring the signs of uterovaginal prolaps (Salmon et al , 1941, Siegel et al , 1962, Eckerling and Goldman, 1972)

On the other hand, data reported on changes in the closure mechanism of the female urethra induced by estrogens and progesterone are conflicting Jeffcoate (1965) noted that continuous administration of estrogen and progesteron preparations might induce stress incontinence He also observed that symptoms of stress incontinence were more prominent during the premenstrual period when levels of steroid hormones were high Caine and Raz (1973) and Faber and Heidenreich (1977) have demonstrated improvement of symptoms when postmenopausal women with stress incontinence were treated with estrogens together with a concomitant increase in urethral closure pressure Patients treated with a progesterone derivative became worse and showed a corresponding decrease in urethral closure pressure (Caine and Raz, 1973) Schreiter et al (1976), using a water perfusion technique, observed an increase in urethral length and pressure measurements in the course of the menstrual cycle in 5 continent women These values decreased prior to the onset of menstruation However, a possible relationship between the changes in urethral pressure profile variables and hormonal changes could not be established since steroid levels were not determined simultaneously Rud (1980b), studying 6 women three times during the menstrual cycle with a recording technique similar to the one used in the present study, could not demonstrate a definite correlation between changes in urethral pressure profile variables and circulating estrogen and progesterone levels during the menstrual cycle In a double blind clinical trial, Walter et al (1978) observed no statistically significant changes in urethral closure pressure and functional urethral length between estrogen-treated and placebo treated postmenopausal women Rud (1980c) treated a group of postmenopausal women, the majority of whom were suffering from urinary incontinence, with high doses of estrogens and found a significant increase in functional urethral length and anatomic urethral length after the estrogen therapy, whereas the urethral closure pressure did not change significantly However, 17 of 24 patients who were suffering from urinary stress incontinence reported a subjective improvement in their symptoms There was no correlation between the subjective improvement and the changes in the urethral pressure profile variables In addition, no difference in effect was observed

between patients treated with estriol and those treated with estradiol Hilton and Stanton (1982c), also, observed significant subjective alleviation in the symptoms of stress incontinence, urgency, and voiding difficulty in response to administration of estrogen cream intravaginally In accordance with Walter et al (1978) and Ek et al (1979), Hilton and Stanton (1982c) observed no significant changes in the variables of the resting urethral pressure profile During stress, however, in the women treated with estrogens improvement in transmission of pressure at the level of the midurethra was observed (Rud, 1980c, Hilton and Stanton, 1982c) Comparing urethral pressure profile variables in different age groups, Rud (1980b) found a gradual decrease in maximum urethral pressure and urethral closure pressure with increasing age, and urethral length was significantly shorter in postmenopausal women than in premenopausal women The decrease in urethral pressure with increasing age has also been observed by other investigators using various techniques (Enhorning, 1961, Edwards and Malvern, 1974, Asmussen, 1975, Obrink et al , 1977, Banninger et al , 1980, Plante and Susset, 1980) However, it has not been proved conclusively that the decrease in urethral pressures after menopause is the result of the decline in the levels of circulating estrogens It was noted earlier that deflections synchronous with the arterial pulse could often be seen superimposed on the urethral pressure recordings These deflections represent vascular pulsations transmitted from blood vessels in and surrounding the urethral wall (Rud et al , 1980) Resnik et al (1974) and Rosenfeld et al (1976) have demonstrated in sheep that estrogens, especially 17β-estradiol, cause considerable vasodilatation and increased blood flow to reproductive organs, to organs within the pelvic cavity (e g cervix and vagina), as well as to mammary glands and skin The increase in peripheral blood flow is paralleled by an increase in cardiac output Molnar and Nagy (1965) demonstrated a fourfold increase in the lumen of the vascular bed in the urethral wall after estrogen treatment Iosif et al (1981a) demonstrated the presence of estrogen receptors in the wall of the female urethra These observations indicate that the urethra is an estrogen-sensitive structure Consequently, it seems reasonable to infer that variations in the amplitude of the pulsations recorded in the urethral wall within the same subjects may reflect variations in the levels of circulating estrogens The increase in amplitude with increasing levels of estradiol ranged from 2 to 6 cm H_2O This may represent a considerable increase in the degree of hyperaemia of the urethral and periurethral vessels and may be sufficient to account for the observed increase in urethral length (Fig 6 4) These observations lead one to conclude that part of the bene-

ficial effect of estrogen therapy in postmenopausal women who are suffering from urinary incontinence can be explained by the stimulating effect of estrogens on the urethral mucosa and on the urethral vascular bed (Berkow, 1953)

In addition to the effects on the vascular bed in the urethral wall, estrogens appear to increase the sensitivity of the alpha-adrenoceptors in the female urethra, thus enhancing the alpha-adrenergic response of the urethral smooth muscles (Schreiter et al , 1976, Ek et al , 1980, Beisland et al , 1981) It has been shown in dogs that progestins facilitate the beta-adrenergic response (Raz et al , 1973) Pharmacologic and clinical studies indicate that in the human there is a predominance of alpha-adrenoceptor sites on the smooth muscle cells in the bladder neck and along the entire length of the urethra, whereas beta adrenergic receptor sites are sparse in the human bladder neck and urethral wall (Ek et al , 1977b) Thus, the anatomic differences in the distribution of these receptors would lead one to anticipate a greater effect of estrogens than of progesterone on the urethra and bladder neck The present observations, indeed, do not support any effect of progesterone on the urethral pressure profile variables There were no significant changes in urethral pressure profile values between the midcycle and early luteal phase measurements, whereas progesterone increased, on an average, sevenfold between these two cycle times

Differences between successive measurements of the same parameter in the same subject may result from a number of factors, including methodologic inconsistencies, instrumental errors and biologic variables Performance of the urethral pressure profile measurements under strictly standardized conditions minimizes the variation due to instrumental and methodologic errrors It is likely that any instrumental and methodologic errors would be randomly distributed over the 27 menstrual cycles The observed individual coefficients of variation show a fairly large variability in especially the pressure variables, which is not systematically related to the items included in the protocol In contrast, it appears that most of the variability in the length variables can be accounted for on the basis of changes systematically and consistently related to the changing levels of E_2 during the menstrual cycle

6 6 SUMMARY

The results of the present study demonstrate that the urethral pressure profile, within the same subject, shows a consistent picture at different

times during the menstrual cycle Urethral length increased systematically with increasing serum levels of E_2 The absolute increase was small, corresponding to 6% of the early follicular phase value, but this effect was very consistent Although the mean intraurethral and mean intravesical pressures of all 27 women hardly varied during the menstrual cycle, pressure amplitudes in successive recordings within one woman may show a fairly wide variaton There is no evidence that urethral pressures at rest are systematically correlated with changes in E_2 and P levels within the range observed during the menstrual cycle Estrogens increase cardiac output and cause considerable vasodilation in the pelvic organs The increase in serum levels of E_2 during the menstrual cycle was paralleled with an increase in amplitude of the vascular pulsations in the urethral wall With the exception of a positive relationship between weight and anatomic urethral length, neither the weight nor the height of the woman seems to be correlated with the urethral pressure profile and related urodynamic variables

The reproducibility of the urethral pressure measurements during the menstrual cycle was similar to that obtained during the pill cycle (chapter 5) The greater variability of the length measurements observed during the menstrual cycle can be accounted for on the changing levels of circulating estrogens

The urethral pressure profile (UPP) in pregnancy and after delivery in healthy nulliparous women

7.1. INTRODUCTION

Pregnancy and delivery are assumed to play an important role in the pathogenesis of lower urinary tract symptomatology (Ullery, 1953, Francis, 1960, Bayer, 1963, Beck and Hsu, 1965, Brown, 1978, Stanton et al , 1980, Iosif, 1981) Alterations in hormone levels, the mechanical pressure exerted by the pregnant uterus, and the passage of the newborn infant through the birth canal may each have its effect on the bladder and urethra The recent introduction of refined techniques for simultaneously measuring pressures in the bladder and in urethra has made it possible to obtain safely extensive and precise information on physiologic and pathologic changes in the lower urinary tract The aims of the present study were to investigate the following

a) changes in the urethral pressure profile (UPP) during pregnancy,

b) whether the changes are related to alterations in blood levels of 17β-estradiol (E_2), progesterone (P), and 17α hydroxyprogesterone (17-OH-P)

c) to what extent obstetric factors affect the urethral pressure profile post partum specifically, vaginal delivery versus cesarean section and, in case of vaginal delivery, duration of the second stage of labor, the presence or absence of an episiotomy, and the birth weight of the neonate,

d) the response of bladder pressure and the urethral closure pressure to stress (i e. coughing) during pregnancy and post partum, and

e) the effects of the first pregnancy and delivery on the urethral pressure profile variables.

Throughout this chapter the letters a) to e) will be used to refer to the aims listed above

7.2. SUBJECTS AND METHODS

7.2.1. SUBJECTS

Forty-three healthy nulliparous women between 20 and 35 years of age participated in this investigation. None was suffering from lower urinary tract symptomatology, and none took medication. Thirty-nine women were primigravid, and four had a history of an early spontaneous abortion. Accurate dating of the pregnancy and the presence of an embryo were confirmed by ultrasound examination at about 8 weeks' amenorrhea. The clinical data of pregnancy and delivery of the 43 women are given in table 7.1. Thirty-seven women underwent delivery at term, and six women underwent delivery prematurely (33 to 37 weeks).

Delivery was vaginal in 36 women and by cesarean section in seven women. Of the 36 vaginal deliveries, five were by forceps, and two were by vacuum extraction. Apart from local anaesthesia for episiotomies, no analgesia was given. Of the seven women who had delivery by cesarean section, two underwent elective cesarean section at 35 and 37 weeks, respectively, because of fetal growth retardation. Four women underwent cesarean section early during the first stage of labor: two because of breech presentation and two because of fetopelvic disproportion. In these six women, the presenting part was not engaged at the time the cesarean section was performed. In the one other patient, the cesarean section was carried out after a failed trial of vacuum extraction with episiotomy after more than 1 hour of second-stage of labor. The post-partum measurements in this woman are not included in the statistical analysis.

TABLE 7.1. Clinical data from the study population.

VARIABLE	MEAN ± S.D.	RANGE	
Age (years)	27.8 ± 3.5	20 - 35	
Duration pregnancy (weeks)	40 ± 2	33 - 42	
Duration 1st stage (hours)(N = 39)	7.3 ± 3.4	2 - 16	
Duration 2nd stage (min.) (N = 36)	37 ± 22	4 - 90	
Birth weight (grams)	3150 ± 590	1240 - 4100	
Delivery	Vaginal		36
	breech	2	
	low forceps	5	
	vacuum extraction	2	
	Cesarean section (before or early in labor)		6
	Cesarean section (2ndstage)		1

The average weight at 8 weeks' amenorrhea was 59 ± 7 (SD) kg, and the mean increase in weight up to the thirty sixth week of pregnancy was 10 ± 2 kg (range, 5 to 17 kg), whereas the average weight at 8 weeks post partum had returned to the value observed at 8 weeks' amenorrhea (differences ranged from −6 to +4 kg) Blood pressures during pregnancy and post partum were normal The distribution of birth weights of the 43 neonates was similar to the distribution of birth weights in our hospital and is shown in Table 7 2 according to percentiles of weight for gestational age (KLOOSTERMAN, 1970)

TABLE 7 2 Birth weight according to Kloosterman s percentiles

Perc	2 3	2 3 5	5 10	10 25	25 50	50 75	75 90	90 95	95
No	2		2	6	13	13	6		1

7 2 2 METHODOLOGY

In each woman simultaneous urethrocystometry, according to the technique described in chapter 4, was performed serially at about 8, 16, 28 and 36 weeks' gestation, and at 8 weeks after delivery Because of premature delivery or for personal reasons, urethral pressure profile recordings at 36 weeks were not performed in seven subjects
The effect of stress on the urethral pressure profile in this study was evaluated by registering urethral pressure profiles under repeated cough provocation Cough profiles were recorded with the pressure transducer at the tip of the catheter located in the bladder, while the proximal pressure transducer at 6 cm from the tip was gradually withdrawn from the bladder through the urethra The urethral closure pressure under stress was measured at the approximate point of maximum urethral pressure

At each study session blood samples were taken for determination of E_2, P, and 17-OH-P by radioimmunoassay as described in chapter 4 Urine cultures were performed at regular intervals, and the cultures were consistently negative No antibiotic prophylaxis was given

The results of the changes in urethral pressure profile variables during pregnancy and after delivery were compared with the values of the urethral pressure profile variables obtained from 27 healthy nulliparous women, of the same age, studied in the early follicular phase of the menstrual cycle under similar conditions (chapter 6)

The study was approved by the Committee for Experimental Research in Human Subjects (Catholic University, Nijmegen, The Netherlands)

7 3. STATISTICAL ANALYSIS

7 3 1 MISSING VALUES

At weeks 8, 16 and 28 there were missing values of one or more urethral pressure profile variables for one (not the same) subject At week 36, data were missing for seven women four in the vaginal delivery group and three in the cesarean section group
The E_2 and P data were incomplete for five subjects during pregnancy, and for four subjects post partum (one missing value in each case) In 11 subjects a value of 17-OH P was missing

7 3 2 STATISTICAL METHODS

With regard to aim a), the changes in each of the urethral pressure profile variables separately for the times 8 versus 16 weeks, 16 versus 28 weeks, 28 versus 36 weeks, and 8 versus 36 weeks were judged by a multiple comparison procedure based on the Bonferroni inequality For each of the four comparisons specified, a (Student) t test for the paired case (ARMITAGE, 1971) was performed and the two-sided p value was calculated Those mean changes for which the corresponding p value was less than 0 05/4 = 0 0125 were considered to be statistically significant This procedure protects against too ready rejection of the null hypothesis
For aims b), c), and d), the procedure outlined above as well as the Kendall rank correlation method and the t test for the paired and unpaired case, were used The methods used are specified in the appropriate text or table
In assessing the significance of differences between the mean values of the urethral pressure profile variables in the group of 36 primiparous women 8 weeks after vaginal delivery and in the 27 nulliparous women studied earlier (aim e of this study) one has to allow for four women common to both groups Therefore, we calculated an estimate of the difference in mean values of each variable by combining the difference in mean values from the paired and unpaired comparisons with the use of the reciprocals of their respective variances as weighting factors Dividing this estimate by its standard error led to an approximately normally distributed test statistic for judging the significance of the estimated difference
A mean, standard deviation (SD), or standard error of the mean (SEM) is given to one decimal place when its value is less than 10

7.4. RESULTS

7.4 1. CHANGES IN URETHRAL PRESSURE PROFILE VARIABLES DURING PREGNANCY (A)

A statistically significant increase during the course of pregnancy was established for the anatomical urethral length, the total bladder pressure and the maximum urethral pressure (Table 7.3 , Figs. 7.1. and 7.2.). The mean total bladder pressure and mean maximum urethral pressure increased almost in parallel. During the course of pregnancy, the increase in the mean total bladder pressure, i e , the difference between the mean values in week 36 and week 8, was 12 cm H_2O in the supine position and 15 cm H_2O in the sitting position. For the maximum urethral pressure these values were 10 cm H_2O and 13 cm H_2O, respectively. In agreement with these findings the mean urethral closure pressure did not change significantly during pregnancy (Table 7.3., Fig. 7 1).

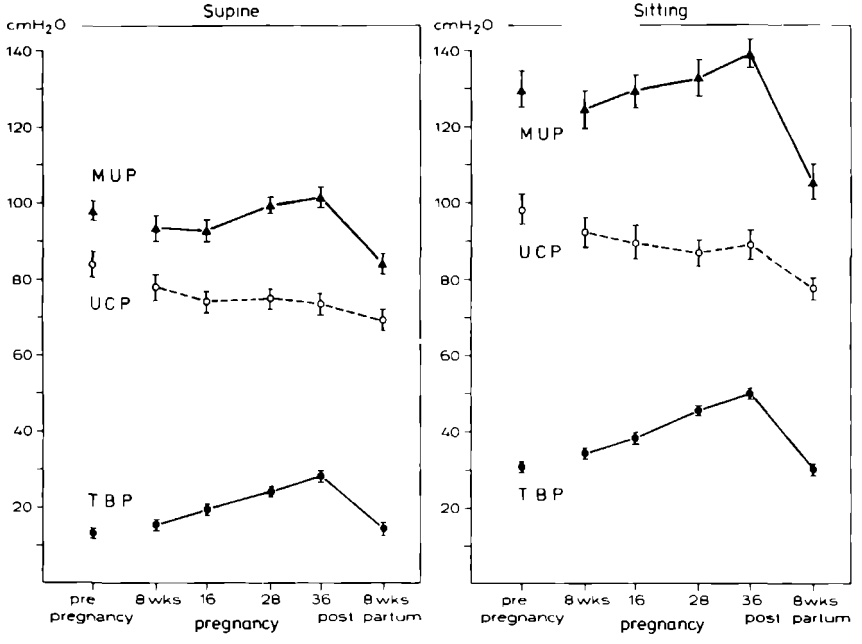


Figure 7 1 Mean values ± SEM of urethral pressure variables during pregnancy and at 8 weeks post partum in the supine and sitting positions Values presented for the group of vaginal deliveries only Prepregnancy values obtained earlier in a group of nulli parous women are given for comparison MUP, maximum urethral pressure, UCP, urethral closure pressure, TBP, total bladder pressure

TABLE 7 3 Judging changes in urethral pressure profile (UPP) variables during pregnancy

UPP variables		Differences between week 36 week 8 mean + SEM		Two sided p values according to the t test for the paired case							
				week 8 16		week 16 28		week 28 36		week 8 36	
		supine	sitting	supine	sitting	supine	sitting	supine	sitting	supine	sitting
length	FUL	− 0 7 ± 0 6	0 0 + 0 9	0 93	0 06	0 29	0 79	0 04	0 26	0 24	0 98
in mm	AUL	+ 3 7 ± 0 5	+ 4 4 ± 0 7	0 02	0 02	0 001	0 001	0 43	0 01	0 001	0 001
	PMP	+ 0 1 + 0 5	+ 0 9 + 1 0	0 25	0 25	0 73	0 84	0 36	0 97	0 78	0 39
pressures	TBP	+ 12 ± 0 7	+ 15 ± 1 1	0 01	0 01	0 001	0 001	0 001	0 001	0 001	0 001
in cm H_2O	MUP	+ 10 ± 2 2	+ 13 ± 3 0	0 90	0 50	0 001	0 02	0 03	0 03	0 001	0 001
	UCP	− 2 1 ± 2 2	− 1 9 ± 3 1	0 05	0 22	0 05	0 22	0 57	0 21	0 44	0 53
	IP	+ 10 ± 26	+ 9 0 ± 4 8	0 18	0 59	0 16	1 00	0 91	0 72	0 70	0 85

A mean is considered to be statistically significant if the corresponding p value is less than or equal to 0,05/4 = 0,0125

With regard to urethral length measurements, the anatomic urethral length gradually increased by approximately 4 mm as pregnancy progressed, whereas the functional urethral length and the distance from the internal meatus to the point of maximum pressure did not change significantly (Table 7.3., Fig. 7.2.). Engagement of the presenting part at 36 weeks did not substantially influence the urethral pressure profile measurements at this time of pregnancy (Table 7.4.).

An increase in the amplitude of transmitted vascular pulsations recorded from the urethral wall was also observed during pregnancy, with the increase being most prominent during the first 16 weeks. The amplitude of the increase ranged from 2 to 10 cm H_2O. After 28 weeks, a tendency toward a decrease in the vascular pulsations was observed.

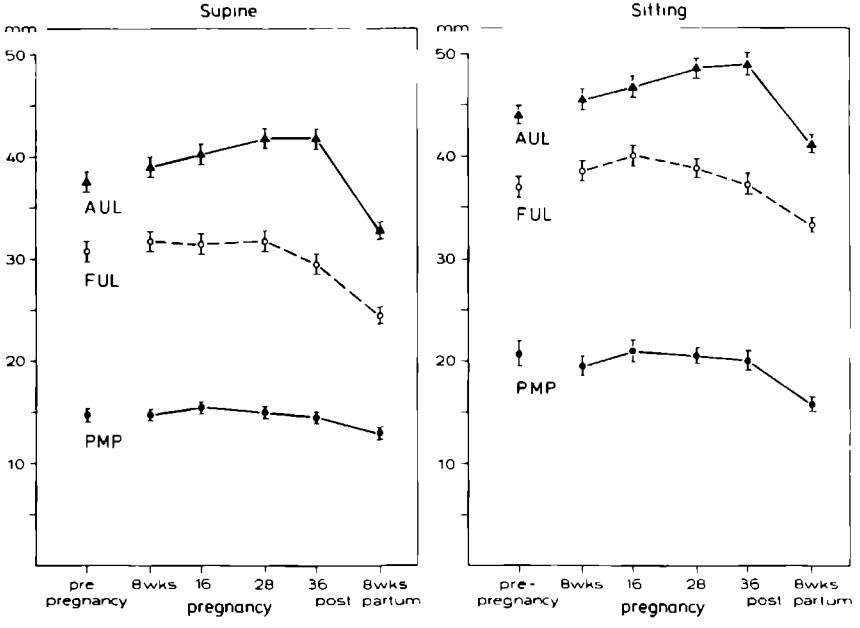


Figure 7.2 Mean values ± SEM of urethral length variables during pregnancy and at 8 weeks postpartum in the supine and sitting positions. Values presented for the group of vaginal deliveries only. Prepregnancy values obtained earlier in nulliparous women are given for comparison with postpartum values. AUL, anatomic urethral length, FUL, functional urethral length; PMP, distance from the internal meatus to the point of maximum pressure.

TABLE 7 4 Mean ± SD of urethral pressure profile (UPP) variables at 36 weeks amenorrhea according to engagement of the presenting part for the women who underwent vaginal delivery

UPP variables	Supine			Sitting		
	Engaged n 11	Not engaged n – 21	p* values	Engaged n = 11	Not engaged n = 20	p* values
FUL	29 + 5 5	30 ± 4 8	0 82	38 ± 7 4	37 ± 5 5	0 79
AUL	40 ± 4 4	42 ± 6 0	0 35	49 ± 4 9	49 ± 7 0	0 89
PMP	15 ± 3 4	14 ± 2 6	0 25	44 ± 5 2	20 ± 6 1	0 96
TBP	27 ± 3	29 ± 4	0 22	50 ± 7	50 ± 5	0 97
MUP	96 ± 17	104 ± 15	0 18	137 ± 22	140 ± 22	0 67
UCP	69 + 18	76 ± 14	0 23	86 ± 25	90 ± 20	0 64
IP/10	58 ± 15	66 ± 17	0 22	97 ± 40	100 ± 33	0 77

* t test for the unpaired case

7 4 2 CORRELATION BETWEEN THE CHANGES IN HORMONE LEVELS AND CHANGES IN URETHRAL PRESSURE PROFILE VARIABLES DURING PREGNANCY (B)

During pregnancy, average E_2 levels increased from 1300 pg/ml at 8 weeks to 34000 pg/ml at 36 weeks P levels increased from 24 ng/ml at 8 weeks to 150 ng/ml at 36 weeks The amount of 17 OH-P in serum was relatively small and showed a gradual increase from 2 9 ng/ml at 8 weeks tot 6 3 ng/ml at 36 weeks These findings are in agreement with the results presented in literature for normal pregnancies (TULCHINSKY et al , 1972, FUCHS AND KLOPPER EDS , 1977) and with serum levels of E_2 and P, determined in normal women from our hospital population throughout pregnancy (THOMAS et al , 1977) Changes in the urethral pressure profile va riables were tested for their correlation with the changes in hormone levels by means of Kendall's rank correlation method This was done for each of the periods 8 versus 16 weeks, 16 versus 28 weeks, 28 versus 36 weeks and 8 versus 36 weeks This resulted in 168 separate correlation coefficients (two positions × four periods × three hormones × seven urethral pressure profile variables) In only four of these 168 correlations was the resulting p value below 0 05 and none of these cases involved significant changes in the urethral pressure profile variables as presented in Table 7 3 This analysis, therefore, yielded no evidence for any correlation between

the changes in urethral pressure profile variables and hormone levels. The changes in the mean levels of E_2, P and 17-OH-P for the 43 women are shown in Fig. 7.3.

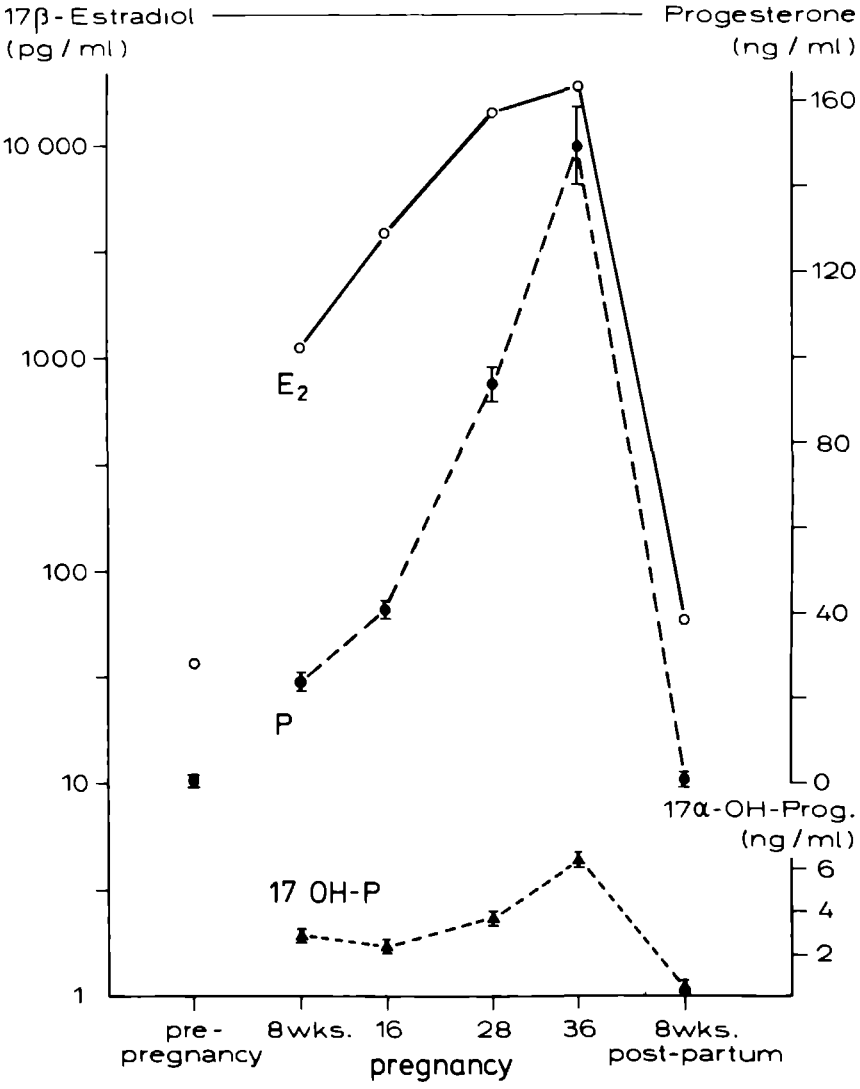


Figure 7 3 Hormone levels at the four times of pregnancy and at 8 weeks post partum. Hormone levels in the early follicular phase of the menstrual cycle obtained earlier in 27 nulliparous women are given for comparison Values are mean ± SEM.

7.4.3. CHANGES IN URETHRAL PRESSURE PROFILE VARIABLES POST-PARTUM (C)

7.4.3.1. VAGINAL DELIVERY VERSUS CESAREAN SECTION

A post partum change is here defined as the differences in urethral pressure profile variables at 36 weeks' gestation and 8 weeks post partum. Unfortunately, for only three out of the six women who underwent delivery by cesarean section early during the first stage of labor were values available of the urethral pressure profile variables at 36 weeks of pregnancy. Thus, the number of subjects in the cesarean section group was too small to permit meaningful comparison of the effects of vaginal delivery and cesarean section on the postpartum changes. It may be noted here that there were no differences with regard to the mean values of the urethral

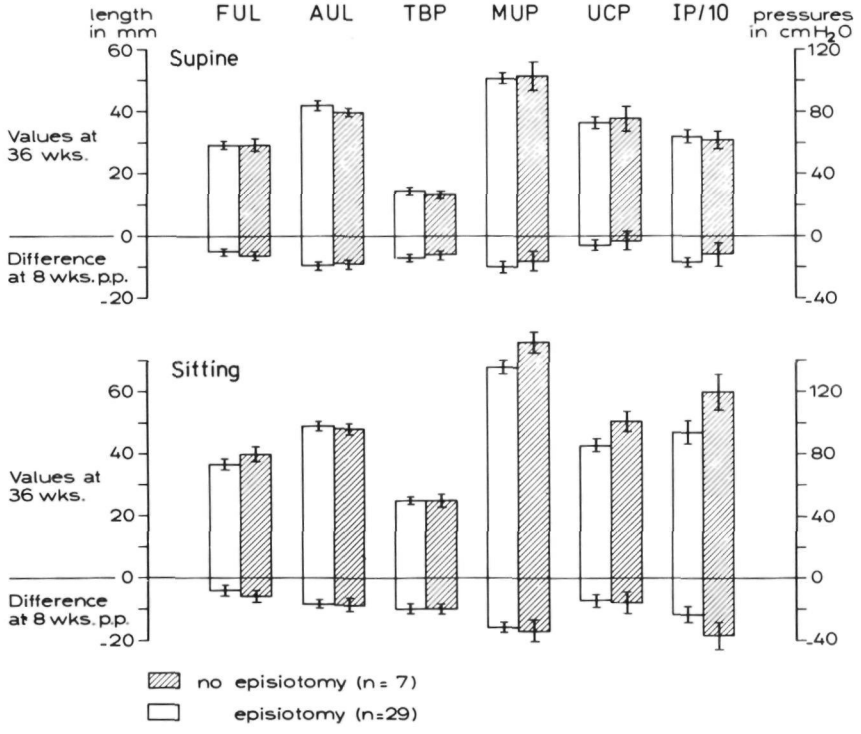


Figure 7.4. Values of urethral pressure profile variables at 36 weeks of pregnancy and their differences at 8 weeks post partum according to the presence or absence of an episiotomy. IP/10 is the integrated urethral closure pressure divided by 10.

pressure profile variables during pregnancy between the women who underwent vaginal delivery and those who underwent cesarean section (t test for the unpaired case, 54 of 56 – two positions × four periods × seven urethral pressure profile variables – comparisons resulted in $p > 0.05$)

7.4.3.2 INFLUENCE OF THE DURATION OF THE SECOND STAGE OF LABOR EPISIOTOMY AND INFANT BIRTH WEIGHT

There was no evidence that in the women with vaginal deliveries the duration of the second stage of labor was correlated with the post-partum changes in urethral pressure profile variables (Kendall rank correlations method 13 of 14 correlation coefficients – two positions × seven urethral pressure profile variables – resulted in $p > 0.10$)

The two groups characterized by the presence or absence of an episiotomy did not show any significant difference in mean changes in the urethral pressure profile values post partum (Fig. 7.4) (t test for the unpaired case, all 14 p values > 0.20)

The birth weight of the neonate did not correlate significantly with the postpartum changes in urethral pressure profile variables in the women who underwent vaginal delivery (Kendall rank correlation method 13 of 14 correlation coefficients resulted in $p > 0.07$)

7.4.4 INFLUENCE OF STRESS ON THE URETHRAL PRESSURE PROFILE DURING PREGNANCY AND AFTER DELIVERY (D)

The mean pressure increase in the bladder during coughing and the simultaneous effect on the urethral closure pressure at the level of the mid-urethra, measured both in the supine and in the sitting positions, are given in Table 7.5.A + 7.5.B and illustrated in Figure 7.5.A + 7.5.B. The mean increase in total bladder pressure as a result of coughing did not change significantly (multiple comparison method) during pregnancy and, averaged for the four measuring times, was 73 cm H_2O in the supine position and 80 cm H_2O in the sitting position. The mean urethral closure pressure during coughing also did not change significantly (multiple comparison method) during pregnancy and was similar to the mean urethral closure pressure at rest in both the supine and sitting positions. The magnitude of the cough induced increase in bladder pressure was smaller post partum than during pregnancy (t test for the paired case $p < 0.001$). For this reason, the effect of stress on the urethral closure pressure post partum cannot be properly assessed (Figs. 7.5.A + 7.5.B). The pattern of transmission of pressure during coughing in successive recordings from the

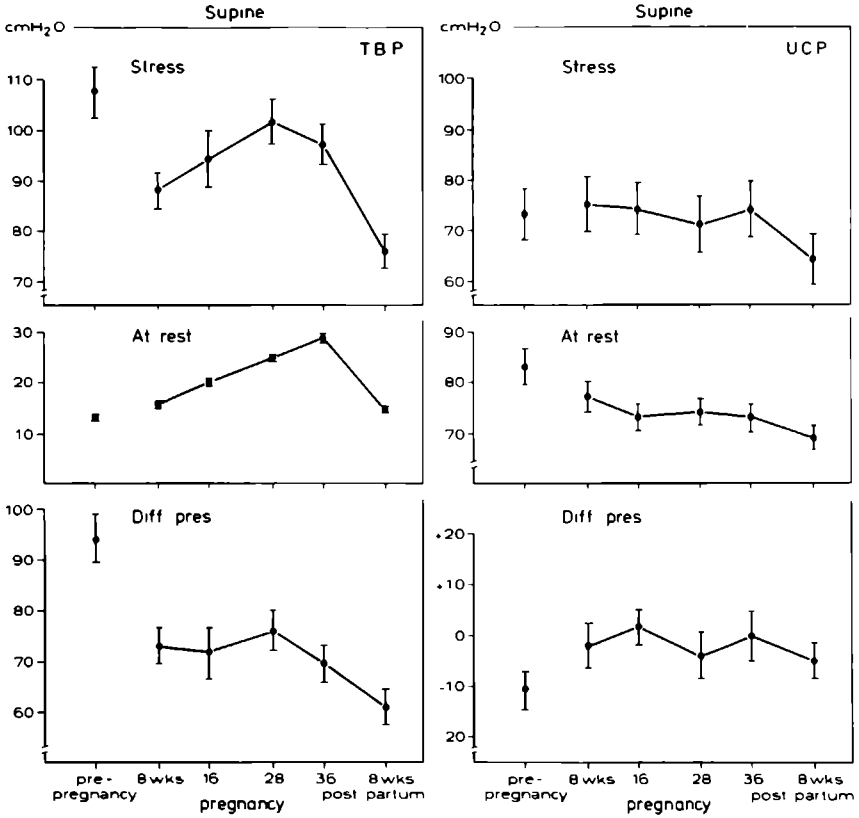


Figure 7.5 A. TBP under stress and at rest and the differences between these two and the UCP under stress and at rest and the differences at the four times of pregnancy and after delivery. Values shown are mean ± SEM.

TABLE 7 5 A. Effect of stress (coughing) on total bladder pressure and urethral closure pressure in the supine position during pregnancy and 8 weeks post partum. Δ TBP and Δ UCP, i.e., peak pressure during cough — resting pressure.

	Δ TBP Stress - rest		Δ UCP Stress - rest	
	n	mean ± SD	n	mean ± SD
8 weeks	32	+73 ± 21	32	−2.1 ± 26
16 weeks	35	+72 ± 29	35	+1.8 ± 20
28 weeks	39	+76 ± 25	39	−4.0 ± 27
36 weeks	31	+70 ± 19	31	−0.2 ± 27
Post partum	41	+61 ± 20	41	−5 2 ± 22

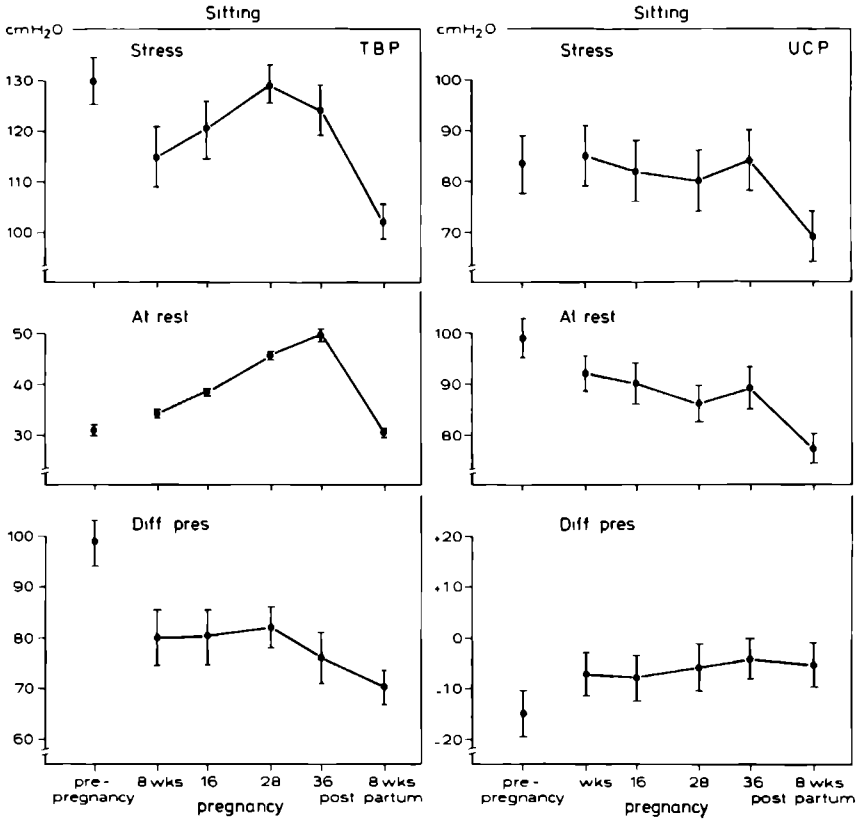


Figure 7 5 B. TBP under stress and at rest and the differences between these two and the UCP under stress and at rest and the differences at the four times of pregnancy and after delivery. Values shown are mean ± SEM.

TABLE 7.5.B Effect of stress (coughing) on total bladder pressure and urethral closure pressure in the sitting position during pregnancy and 8 weeks post partum. Δ TBP and Δ UCP, i.e., peak pressure during cough − resting pressure

	Δ TBP Stress - rest		Δ UCP Stress - rest	
	n	mean ± SD	n	mean ± SD
8 weeks	32	+80 ± 30	32	−7.3 ± 24
16 weeks	35	+80 ± 33	35	−1 8 ± 27
28 weeks	39	+82 ± 24	39	−6.0 ± 27
36 weeks	31	+76 ± 28	31	−4.2 ± 21
Post partum	41	+70 ± 22	41	−5.4 ± 26

individual subjects was not consistently altered during the course of pregnancy In nine women, during a cough, the pressure in the urethra increased more than that in the bladder, thereby resulting in an increased urethral closure pressure In 12 women, a defective transmission of pressure to the functional urethra resulting in a decreased urethral closure pressure during stress was observed In the remainder of the individuals, the urethral closure pressure during coughing changed minimally during pregnancy

7 4 5 URINARY INCONTINENCE DURING PREGNANCY AND AFTER PREGNANCY

Fourteen women experienced involuntary leakage of urine during pregnancy In 12 women, the symptoms were suggestive of stress incontinence, whereas the complaints were more compatible with unstable bladder contractions in the other two subjects No objective evidence of stress-incontinence or unstable contractions of the detrusor muscle could be *demonstrated during pregnancy*

Post partum, two subjects had objective evidence of stress incontinence, and transient of persistent symptoms of stress incontinence were present in four additional women In five of these six women, the symptoms began during pregnancy One woman experienced symptoms of stress incontinence first in the puerperium In almost all subjects with stress incontinence, the values of the urethral pressure profile variables were below the median values for the study population, and a defective transmission of pressure to the functional urethra was observed in all The distributions of the values of the continence variables functional urethral length, urethral closure pressure, and integrated pressure of the women with subjective and/or objective urinary incontinence during pregnancy and post partum are shown in three frequency histograms for the study population (N = 42) (Figs 7 6 , 7 7. and 7 8)

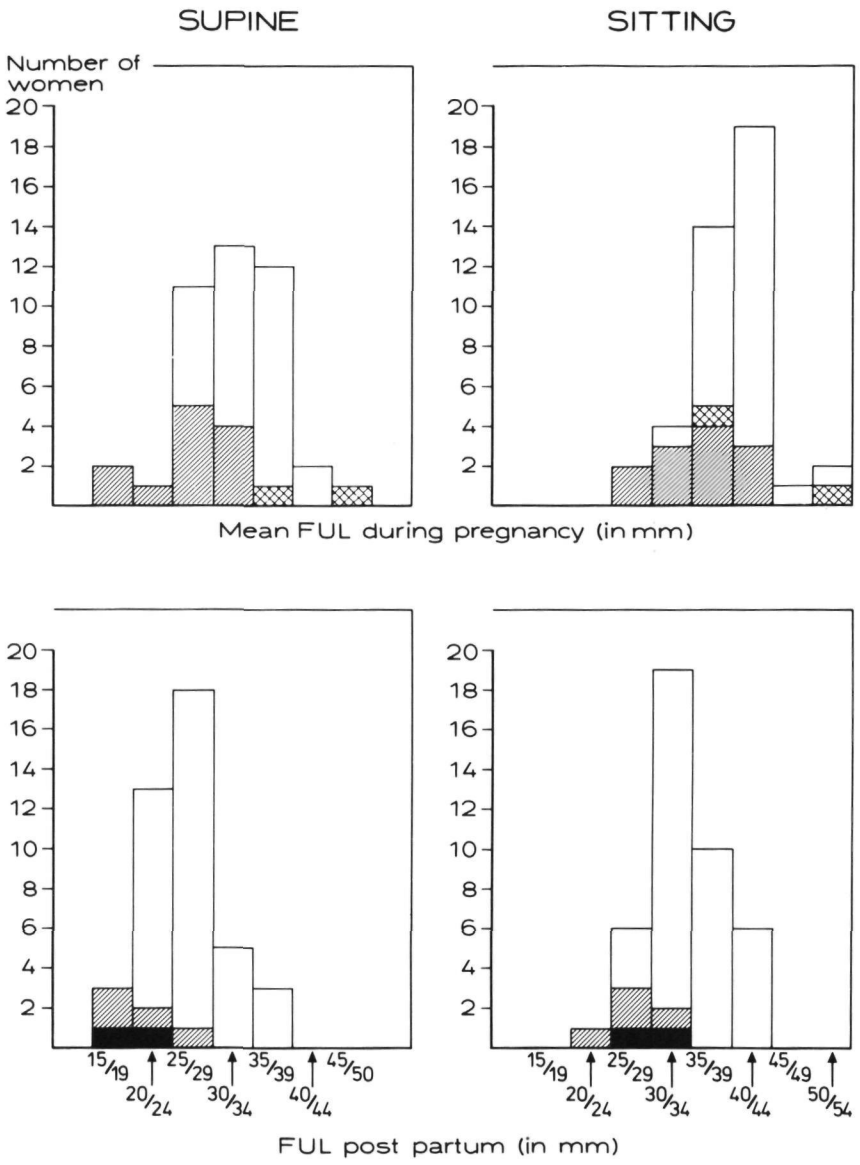


Figure 7.6. Frequency distribution of the values of mean FUL during pregnancy and post partum.

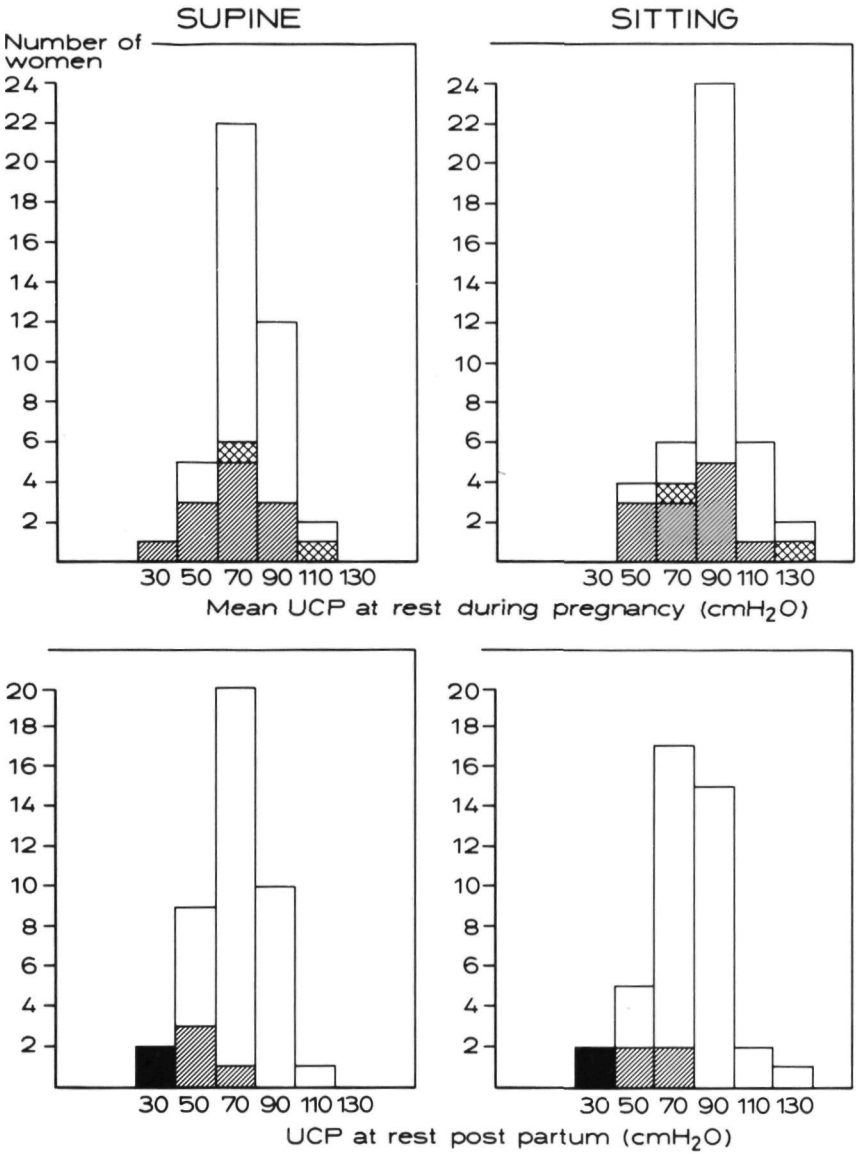


Figure 7.7. Frequency distribution of the values of mean UCP at rest during pregnancy and post partum.

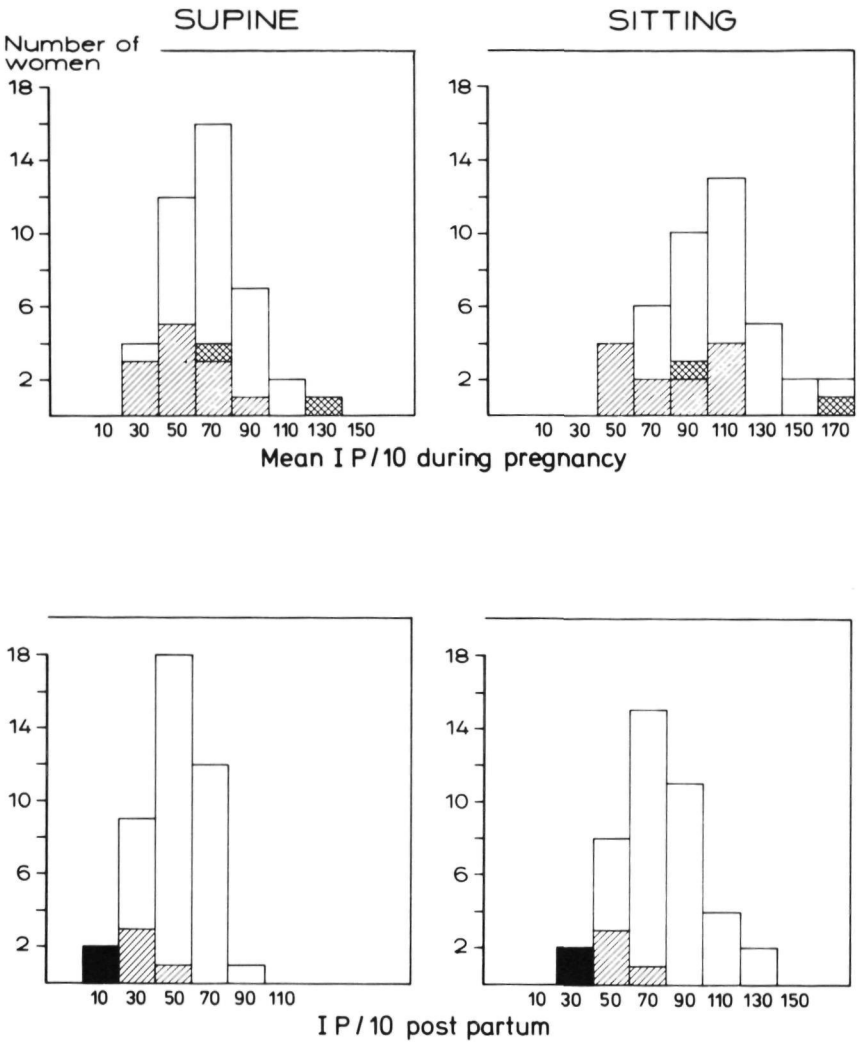


Figure 7.8. Frequency distribution of the values of the mean IP/10 at rest during pregnancy and post partum.

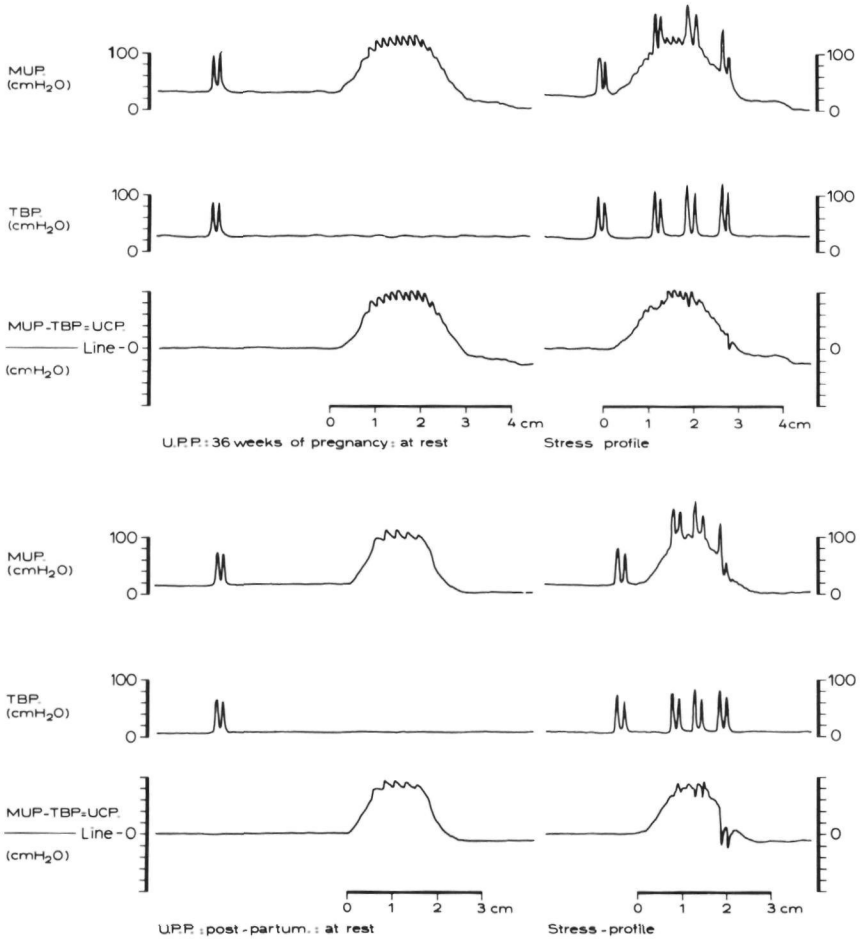


Figure 7.9.A. Urethral pressure profile recordings from a continent subject at 36 weeks of pregnancy and at 8 weeks post partum. In each figure the upper tracing is the MUP, the middle tracing is the TBP, and the lower tracing is the differential pressure, i.e., UCP. A static urethral pressure profile at rest is shown on the left side of each figure and a dynamic urethral pressure profile during coughing is shown on the right.

Figs. 7.9.A and 7.9.B illustrate the pattern of the urethral pressure profile and of transmission of pressure in a normal subject (Fig. 7.9.A) and in a woman with stress incontinence (Fig. 7.9.B) during pregnancy and post partum.

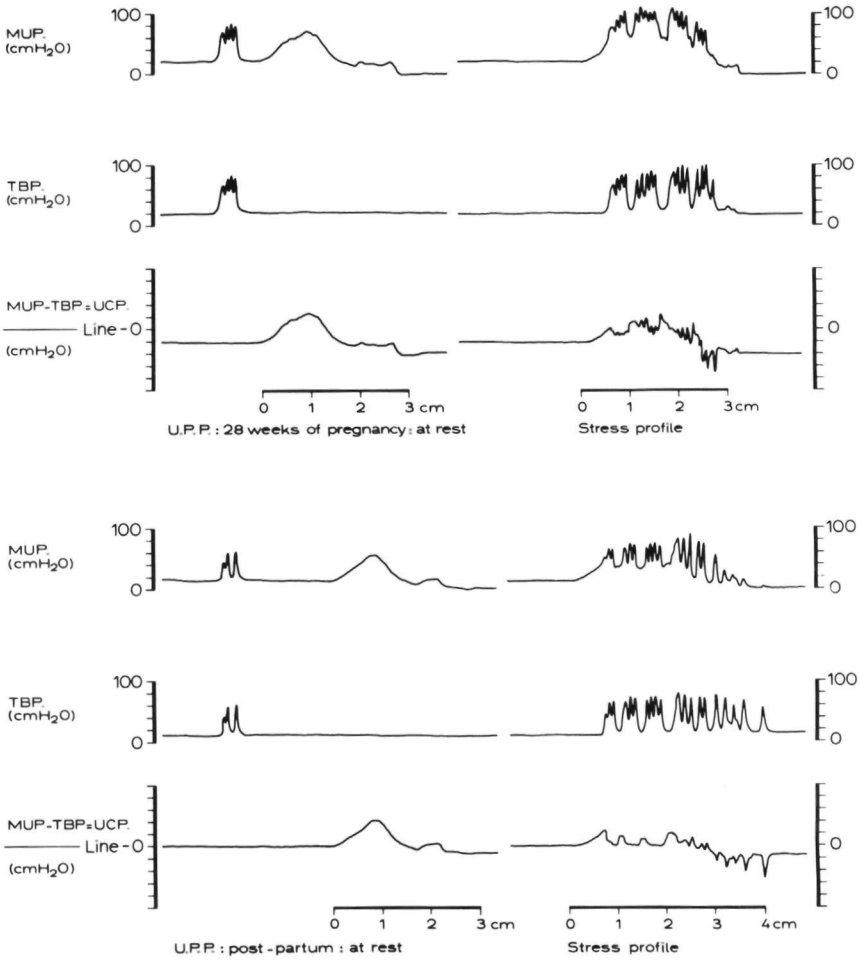


Figure 7.9.B. Urethral pressure profile recordings from a woman with stress incontinence at 28 weeks of pregnancy and 8 weeks post partum. A low urethral pressure profile and defective transmission of pressure are apparent.

7.4.6. EVALUATION OF THE EFFECTS OF FIRST PREGNANCY AND DELIVERY ON THE URETRHAL PRESSURE PROFILE VARIABLES (E)

The mean values of the urethral pressure profile variables at 8 weeks post partum in the women who underwent vaginal delivery were significantly lower than the corresponding mean values of the urethral pressure profile variables in nulliparous women recorded in the follicular phase of the menstrual cycle (VAN GEELEN et al., 1981; chapter 6) (for statistical test, see Statistical methods, page 76).

For the six women who underwent delivery before or early in labor by cesarean section, the urethral length variables 8 weeks post partum were not significantly different from the values in nulliparous women (Table 7.6.). Maximum urethral pressure and urethral closure pressure were significantly reduced post partum in the sitting position; and although the reduction in maximum urethral pressure and urethral closure pressure in the supine position fell short of statistical significance, the average difference between post partum and nulliparous values were similar to those found in the vaginal delivery group (Table 7.6.). In the woman who underwent delivery by cesarean section late in the second stage of labor after a failed trial of vacuum extraction with episiotomy, the postpartum changes were similar to those observed in the vaginal delivery group (Fig. 7.10).

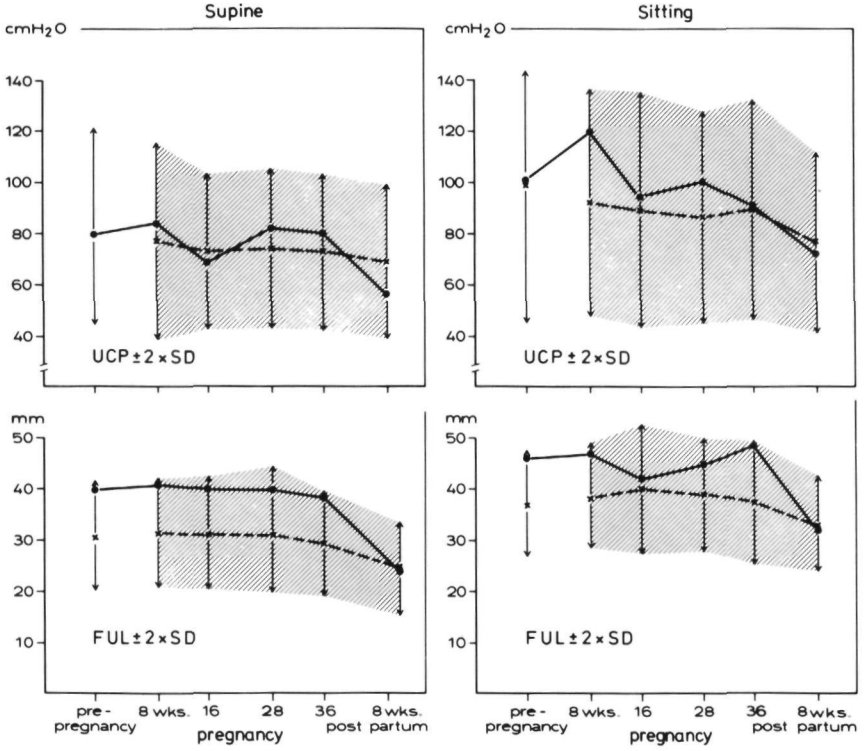


Figure 7.10. Values of FUL and UCP, measured before pregnancy, during pregnancy and at 8 weeks post partum in a woman with complicated delivery: cesarean section after failed vacuum extraction. Mean values (broken line) ± 2 × SD (shaded area) of FUL and UCP for the group of women who delivered vaginally are shown for comparison.

When the mean values of the urethral pressure profile variables at 8 weeks post partum were compared with the mean values at 8 weeks' gestation, all urethral pressure profile variables post partum were significantly decreased in the women who underwent vaginal delivery (t test for the paired case). In the six women who underwent delivery before or early in labor by cesarean section, however, the estimated difference in mean values at 8 weeks post partum and at 8 weeks' amenorrhea was minimal and the pattern of change was not consistent (Table 7.7.A + 7.7.B).

TABLE 7 6 Estimated differences between mean values of urethral pressure profiles (UPP) variables (at rest) of primiparous women 8 weeks post partum and of nulliparous women in the follicular phase of the cycle

UPP variables		Primiparous women, vaginal delivery (N = 36) - nulliparous women (N = 27)			Primiparous women, cesarean section (N = 6) - nulliparous women (N = 27)		
		Estimated difference in mean values	Standard error	Statistical significance p value*	Estimated difference in mean values	Standard error	Statistical significance p value**
Supine	FUL	− 5 3	1 0	0 01	− 1 6	1 7	0 35
	AUL	− 2 8	0 6	0 01	− 2 2	1 7	0 21
	TBP	− 2 4	0 6	0 01	− 0 9	1 2	0 46
	MUP	−13	3 7	0 01	−14	9 8	0 16
	UCP	−14	3 3	0 01	−12	8 8	0 18
	IP/10	−16	3 0	0 01	− 2 0	8 8	0 82
Sitting	FUL	− 3 8	1 1	0 001	− 0 1	1 9	0 96
	AUL	− 2 9	1 0	0 003	− 1 0	1 8	0 58
	TBP	− 0 7	1 2	0 56	− 2 1	2 3	0 37
	MUP	−22	5 2	0 001	−24	9 2	0 01
	UCP	−23	5 1	0 001	−21	9 0	0 03
	IP/10	−24	6 5	0 001	−16	14	0 26

* See statistical methods

** t test for the unpaired case

TABLE 7 7 A Statistics of the urethral pressure profile (UPP) variables at 8 weeks' amenorrhea and 8 weeks post partum Vaginal delivery (N = 36)

UPP variables	8 weeks' amenorrhea × ± SEM	8 weeks post partum × ± SEM	Diff × ± SEM	Number			t test for the paired case Two sided p values
				neg	equal	pos	
Supine							
FUL	31 7 ± 0 9	24 6 ± 0 8	− 6 9 ± 0 7	33	1	1	p < 0 00001
AUL	39 0 ± 0 9	32 8 ± 0 8	− 5 9 ± 0 6	35	–	–	p < 0 00001
TBP	16 ± 1	14 ± 1	− 1 3 ± 0 7	17	10	8	p = 0 064
MUP	93 ± 3	83 ± 3	− 9 ± 3	23	2	10	p = 0 003
UCP	77 ± 3	69 ± 2	− 8 ± 3	19	6	10	p = 0 007
IP/10	70 ± 4	49 + 3	−19 ± 3	32	–	3	p < 0 00001
Stress UCP	75 ± 5	64 ± 5	−11 ± 5	20	–	7	p = 0 051
Sitting							
FUL	38 5 ± 1 0	33 2 ± 0 8	− 5 1 ± 1 0	29	2	4	p = 0 00002
AUL	45 5 ± 1 1	41 1 ± 0 8	− 4 2 ± 0 8	28	2	5	p < 0 00001
TBP	34 ± 1	30 ± 1	− 3 8 ± 0 8	24	8	3	p = 0 00004
MUP	127 ± 4	108 ± 3 0	−18 ± 4	27	–	8	p = 0 00002
UCP	92 ± 4	77 ± 3 0	−15 ± 4	24	2	9	p = 0 0003
IP/10	104 ± 6	75 ± 4	−27 ± 5	30	–	5	p < 0 00001
Stress UCP	85 ± 6	69 ± 5	−19 ± 6	20	1	6	p = 0 004

TABLE 7 7 B Statistics of the urethral pressure profile (UPP) variables at 8 weeks' amenorrhea and 8 weeks post partum Cesarean section (N – 6)

UPP variables		8 weeks' amenorrhea × ± SEM	8 weeks post partum × ± SEM	Diff × ± SEM	Number		
					neg	equal	pos
Supine	FUL	34 2 ± 2 1	32 3 ± 1 4	−1 8 ± 2 3	2	2	2
	AUL	40 2 ± 2 0	39 7 ± 1 5	−0 5 ± 1 3	2	3	1
	TBP	16 ± 2	14 ± 1	−1 3 ± 1 5	3	1	2
	MUP	89 ± 4	84 ± 9	−5 ± 9	5	–	1
	UCP	73 ± 4	71 ± 8	−2 ± 7	4	1	1
	IP/10	71 ± 4	65 ± 8	−6 ± 6	4	–	2
	Stress UCP	77 ± 12 (n = 4)	60 ± 10 (n = 5)	−4 ± 9	2	–	1
Sitting	FUL	38 5 ± 1 4	37 3 ± 1 6	−1 3 ± 1 6	3	1	2
	AUL	45 2 ± 1 4	43 0 ± 1 6	−2 2 ± 1 2	4	2	–
	TBP	31 ± 2	29 ± 2	−2 ± 2 4	3	2	1
	MUP	114 ± 4	107 ± 8	−7 ± 6	5	–	1
	UCP	82 ± 5	78 ± 8	−3 ± 6	3	–	3
	IP/10	93 ± 6	85 ± 12	−8 ± 9	4	–	2
	Stress UCP	79 ± 8 (n = 5)	84 ± 12 (n = 5)	−0 ± 9	2	–	2

7.5 DISCUSSION

Objective data regarding changes which occur in the bladder and urethra during pregnancy and as a result of labor are sparse Simple supine filling cystometry during pregnancy was carried out by MUELLNER (1939) and later by FRANCIS (1960) YOUSSEF (1956) and CLOW (1975) performed cystometry and urethrometry in pregnant women However, the results of these cystrometric studies were not consistent and, therefore, do not allow definite conclusions about the influence of pregnancy and delivery on the physiology of the lower urinary tract Urodynamic studies during pregnancy and in the puerperium with the use of microtransducer catheters for simultaneous urethrocystometry and urethral pressure profile measurements have recently been reported by IOSIF et al , (1980) The recording instrument was similar to that used in the present study

Detailed anatomical studies (HUISMAN, 1979), urethrocystography (WESTBY AND ASMUSSEN, 1981) and urethral pressure profile recordings under stress (ENHORNING, 1961) indicate that, in the normal nonpregnant state, the bladder base and the urethrovesical junction are situated just within the pelvic cavity, on a line joining the lower border of the symphysis with the tip of the sacrum The major part of the functional urethra and the point of maximum urethral pressure are proximal to the urogenital diaphragm During pregnancy and early in labor, the anatomy of bladder neck and urethra and their positions within the pelvis remain unchanged When the presenting part becomes engaged, the bladder neck and proximal urethra are displaced forward and come to lie close behind the symphysis The bladder is compressed against the symphysis. Most of the bladder lies within the abdomen but a small portion remains in the pelvis (MALPAS et al , 1949, KANTOR et al , 1949, COHN AND WEINBERG, 1950) As a consequence, upward movement of the urethrovesical junction and elongation of the urethra are small

Studies on the transmission of pressure in the nonpregnant state have demonstrated that, at rest, total bladder pressure and the pressures in the space of Retzius are almost equal An increase in intra-abdominal pressure (e g , coughing) is transmitted to the bladder and, almost to the same extent, via the pre urethral space to the proximal three quarters of the urethra (ENHORNING, 1961, BJERLE, 1974, OBRINK et al , 1978) In the present study, as well as in the studies reported by CLOW (1975) and IOSIF et al (1980) an increase in total bladder pressure during pregnancy was ob

served The magnitude of the increase in total bladder pressure was similar in the supine and sitting positions The maximum urethral pressure increased in parallel with the total bladder pressure The increases in total bladder pressure and maximum urethral pressure during pregnancy are two to three times the increase in intra-abdominal pressure during pregnancy (approximately 5 cm H_2O) found by CALDEYRO BARCIA (1960) From the anatomic and radiologic studies mentioned above, one may conclude that direct pressure exerted by the growing uterus on the bladder and periurethral structures also contributes to the parallel increase in total bladder pressure and maximum urethral pressure during pregnancy In agreement with these findings, the mean urethral closure pressure and the mean integrated pressure, which reflects the total cumulative urethral resistance, did not change significantly during pregnancy The mean values of urethral pressure and integrated pressure observed in our pregnant subjects were only slightly below the corresponding mean values found in healthy nulligravid women studied earlier (VAN GEELEN et al , 1981, chapter 6)
The results of the measurements of urethral length in this study agree with the anatomic and radiographic observations described above Upward displacement of the urethrovesical junction and elongation of the urethra are small during pregnancy and at the onset of labor (MALPAS et al , 1949, KANTOR et al , 1949) Consequently functional urethral length and the distance from the internal meatus to the point of maximum pressure did not change significantly, whereas anatomic urethral length showed a small but gradual increase of approximately 4 mm up to the thirty sixth week of pregnancy The mean values of functional urethral length in the supine and sitting positions are similar to those found in healthy nonpregnant nulliparous women Urodynamic studies in nonpregnant nulliparous women demonstrated a small but significant increase in anatomic urethral length and functional urethral length which correlated with increasing levels of serum E_2 (VAN GEELEN et al , 1981, chapter 6) The increase in urethral length at midcycle was accompanied by an increase in the amplitude of transmitted vascular pulsations recorded from the urethral wall This observation suggested a causal relationship between the observed changes in urethral length and the degree of urethral and periurethral hyperemia The increased vascular pulsations during pregnancy above the level observed at midcycle were not accompanied by a parallel increase in functional urethral length and anatomic urethral length nor by an increase in urethral closure pressure After 28 weeks, the amplitude of the vascular pulsations decreased These findings suggest that the dilating effect of estrogens on the vascular bed in the urethral and periurethral tissues is

limited In addition, the lack of correlation between hormone levels and changes in urethral pressure profile variables provides no support for the concept that the increasing levels of progesterone and 17 OH P during pregnancy significantly influence the tone of the muscular and elastic tissue in the urethral wall A possible effect of progesterone on the tone of the detrusor muscle was not investigated

The results of the present study lead one to conclude that the continence variables (i e , functional urethral length, urethral closure pressure and integrated pressure) do not change significantly during pregnancy These results are at variance with the observations of Iosif et al (1980) who found an increase in urethral length variables, as well as an increase in urethral closure pressure, during the course of pregnancy in 14 healthy primiparas The study of Iosif et al (1980) was not described in sufficient detail to allow any definite conclusions as to the reason for the differences in the findings between that investigation and the present one
The effect of delivery was evaluated 8 weeks postpartum, when involution of the genital organs is complete and anatomic relationships in the pelvis have been restored to the prepregnancy situation The mean values of the steroid hormone levels observed at 8 weeks post partum were similar to those obtained in healthy nonpregnant women in the early follicular phase of the menstrual cycle (chapter 6)
The total bladder pressure had returned to its prepregnancy level by this time in all women All urethral length and pressure measurements were decreased significantly after vaginal delivery when compared with values at 8 weeks' amenorrhea, and when compared with values in healthy nulli parous women The post partum values were in good agreement with the post partum results obtained by other investigators (Enhorning, 1961, Iosif et al , 1981b) In the six women who underwent cesarean section, however, the urethral length variables were almost equal to those obtained in nulliparous women and in early pregnancy
Radiographic studies have shown that the bladder base and urethrovesical junction are displaced and the supporting structures stretched as labor pro gresses (Malpas et al , 1949, Kantor et al , 1949) The extent of this stretching is dependent upon the relationship between fetal size and pelvic capacity Some trauma is incurred by the bladder and urethra during every instance of labor and delivery, as shown by cystoscopy (Funnel et al , 1954, Seski and Duprey, 1961) The extent of traumatic changes varies from increased edema and mucosal congestion to varying degrees of submucosal hemorrhage, and sometimes, actual capillary oozing These

findings are most marked in the region of the bladder neck and trigone, and around the ureteral orifices The traumatic changes in the bladder wall tend to disappear during the first few post partum days In women who underwent elective cesarean section, only minimal traumatic changes were observed in the postpartum bladder (FUNNEL et al , 1954) The radiographic and cystoscopic observations described above strongly suggest that trauma to the bladder, urethra and supporting musculofascial structures during vaginal delivery is responsible for the postpartum changes in urethral pressure profile measurements

The postpartum changes in urethral pressure profile variables found in this study were not substantially influenced by the duration of the second stage of labor nor by the presence or absence of an episiotomy Nor did the birth weight of the infant correlate with the magnitude of the changes observed post partum The amplitude of the vascular pulsations in the urethral wall in the postpartum recordings was notably decreased in almost all women, who underwent vaginal delivery From these observations, it would appear that the passage of a fetus through the birth canal is the important event, and that the size and the relative ease or difficulty of its passage are of minor importance with regard to the effects on the urethral pressure profile In support of this view are the results of the urethral pressure profile measurements in the woman with a complicated delivery that ultimately resulted in a cesarean section
The post partum changes seem to be permanent Urethral pressure profile measurements recorded in six of these subjects more than 1 year after delivery were similar to those obtained 8 weeks post partum

Urinary continence in the female at rest is maintained by the tone of the urethral smooth musculature and fibro-elastic tissues in urethral wall and bladder neck and by the turgor in the vascular bed in the submucosal layer (ZINNER et al , 1976) The striated voluntary muscle in the urethral wall and in the pelvic floor and the proper transmission of intra-abdominal pressure to the bladder and urethra act as secondary sphincter mechanisms in preventing urinary leakage during stress The contribution of each compo nent to the intra-urethral pressure, at rest or under stress, has not yet been fully elucidated The onset of urinary incontinence is often attributed to pregnancy and/or delivery (FRANCIS, 1960, BECK AND HSU, 1965, IOSIF, 1981) Twelve women (about 25%) of the present study population had subjective symptoms of stress incontinence of varying degree during preg nancy Stress incontinence manifested itself in those women who had

already early in pregnancy demonstrated a low urethral pressure profile and defective transmission of pressure over the urethra. These observations indicate that an inherent weakness of the closure mechanism of the urethral wall and periurethral supporting tissue is an underlying basis for the development of stress incontinence.

7.6. SUMMARY

The following conclusions have been reached on the basis of the present data:

a. The continence variables (functional urethral length and urethral closure pressure and integrated pressure) do not change significantly during pregnancy.
b. The changes in urethral pressure profile variables which do occur during pregnancy are not correlated with alterations in the levels of E_2, P, or 17-OH-P.
c. The postpartum changes in urethral pressure profile after vaginal delivery are not substantially influenced by the duration of the second stage of labor nor by the presence or absence of an episiotomy, nor are they correlated with the birth weight of the infant.
d. On the average, the urethral closure pressure response to stress is not altered during pregnancy. However, in some women who early in pregnancy show a low urethral resistance and defective transmission of pressure, these conditions are accentuated during pregnancy and after delivery, and eventually lead to stress incontinence.
e. Pregnancy followed by a first vaginal delivery results in reduced urethral length and decreased urethral closure pressure.

Summary

The present study was undertaken to investigate the effects of biologic variables and the influences of physiologic alterations on the urethral pressure profile in healthy women.

The urethral pressure profile (UPP) denotes a recording of the intraluminal pressure along the length of the urethra with the bladder at rest. During the last two decades, interest in studying urethral function by recording the urethral pressure profile has grown and has contributed considerably to a better understanding of the mechanisms of continence and micturition. The microtransducer technique for intraluminal pressure measurements has proven to be an accurate and sensitive technique with a high frequency response and has largely replaced the other methods at present. With the use of two microtransducers, mounted within the same catheter at 6 cm distance, simultaneous recording of the intravesical pressure and the urethral pressure profile, i.e., simultaneous urethrocystometry, can be performed.

A short survey of the anatomy and neurophysiology of the lower urinary tract and a description of the urethral pressure profile precede the experimental part of the study.

CHAPTER 1 gives a review of the anatomy of the bladder and urethra.

Three muscle systems constitute the wall of the bladder and urethra, i.e., the detrusor muscle, the trigonal muscle system and the urethral muscle system. For a better understanding of the complex relationships between these muscle systems reference is made to their embryologic development. There is no consensus among the different investigators as to the origin and precise course of the muscle bundles at the level of the bladder neck. Increasing evidence suggests that the detrusor muscle and the urethral muscle system constitute anatomically distinct units. The detrusor muscle consists of a complex meshwork of interlacing smooth muscle

bundles of varying thickness The urethral smooth muscle consists of small muscle bundles embedded in dense fibroelastic collagenous tissue Outside the urethral smooth muscle is the striated urethral muscle, which is most prominent in the ventral and lateral parts of the urethral wall The striated urethral muscle is anatomically separate and morphologically different from the striated muscles in the pelvic floor, which surround the distal part of the urethra The pubo-urethral ligaments which run from the pelvic surface of the os pubis to the anterior urethral wall constitute the suspensory mechanism of the urethra and aid in keeping the urethra in its forward and upward position within the pelvic cavity

CHAPTER 2 describes the neurophysiology of the lower urinary tract

The bladder and urethra are supplied by parasympathetic fibers via the pelvic nerves and by sympathetic fibers via the hypogastric nerves The preganglionic parasympathetic and the pre- and postganglionic sympathetic fibers in the hypogastric nerves form the pelvic and vesical plexuses The ganglion cells in the pelvic and vesical plexuses are of three types exclusively adrenergic, exclusively cholinergic and postganglionic neurons responding to stimulation of either sympathetic or parasympathetic preganglionic input The role of the autonomic system in the mechanisms of continence and micturition has been studied primarily by receptor stimulation and blockade and by electrophysiologic techniques More recently, neurohistochemical and electronmicroscopic techniques have further clarified the pharmacological observations The detrusor muscle is innervated by parasympathetic fibers in the pelvic nerves In the human, the density of these cholinergic nerves decreases distally in the bladder neck and in the urethra In accordance with these observations, the cholinergic innervation of the bladder neck and urethra seems to be of minor clinical importance The adrenergic system plays an important role in the functional control of the bladder and urethra However, the number and distribution of noradrenergic nerve terminals among the smooth muscle bundles in the bladder and urethra is sparse compared to the rich and uniform supply of cholinergic fibers In general, pharmacological studies demonstrate a preponderance of beta-adrenergic activity in the body of the bladder, whereas alpha adrenergic activity predominates in the bladder base and in the urethra The precise mechanisms through which the adrenergic system exerts its influence on the bladder and urethra is not clear The presence of noradrenergic synaptic terminals on postganglionic neurons and the presence of interganglionic connections provide for functional interaction

of the sympathetic and parasympathetic nervous systems in the innervation of the lower urinary tract Gonadal steroids may influence the effects of adrenergic stimulation through interaction with the adrenoceptor system

No consensus exists as to the peripheral innervation of the striated urethral muscle The striated muscles of the pelvic floor receive their innervation by way of the pudendal nerves

The pelvic, the hypogastric and the pudendal nerves are mixed nerves and contain efferent fibers to and afferent fibers from the bladder and urethra The afferent fibers synapse on interneurons and projection neurons in the spinal cord Some fibers pass, without interruption, to the brain stem The complex system of centripetal and centrifugal nerve pathways within the central nervous system may be grouped into 4 distinct neuroanatomic circuits or loops, which act together to permit volitional modulation of reflex bladder control mechanisms at the spinal level

CHAPTER 3 presents a description of the urethral pressure profile (UPP)

A survey of the different techniques for recording the urethral pressure profile and a summary of the clinical value of urethral pressure profile measurements are presented The definitions of the variables of the urethral pressure profile, introduced by the Standardization Committee of the I C S , and the additional variables measured in this investigation, are given

Under normal conditions, during the filling phase of the bladder, the closure function of the bladder neck and proximal urethra is mainly determined by the sympathetically innervated smooth muscle systems at the bladder outlet together with the tension exerted by the fibroelastic tissue surrounding the smooth muscle bundles At midurethra and in the distal part of the functional urethra urethral smooth muscle combines with the urethral and periurethral striated muscles to maintain adequate urethral closure pressure The spongy, easily compressible structure of the inner urethral wall, composed of mucosa and submucosa, provides under external compression a watertight seal within the urethral lumen

During stress (e g coughing) and physical effort, the increase in intra-abdominal pressure is transmitted to the bladder and almost to the same extent to the intrapelvic portion of the urethra During stress, active contraction of the striated urethral and periurethral muscles further reinforces urethral closure pressure at midurethra and at the level where the urethra traverses the pelvic floor

CHAPTER 4 describes the aims of the study and the methodology employed

The aims of the study were to investigate the effects of biologic variables and the influences of physiologic alterations, i e , hormonal changes, pregnancy and delivery, on the urethral pressure profile
Simultaneous urethrocystometry, which includes recording of the intravesical pressure and the urethral pressure profile, was performed with the use of the microtransducer technique The measuring device, the calibration procedure and the measuring technique are described All recordings were performed according to a precise and standardized methodology in healthy women between 18 and 35 years of age Prior to each recording session blood samples were taken for hormonal determinations A description of the determinations of the serum levels of follicle stimulating hormone (FSH), luteinizing hormone (LH), prolactine, 17β-estradiol (E_2), progesterone (P) and 17α-hydroxyprogesterone (17-OH-P) is given

CHAPTER 5 describes the reproducibility of urethral pressure profile measurements with the microtransducer technique in a group of healthy nulliparous women

Estimation of the short term reproducibility as well as investigation of which of several serially recorded urethral pressure profiles can be considered as most representative of the basal condition, was carried out by performing multiple urethral pressure profile recordings within the same study session in twelve women Estimation of the long term reproducibility and investigation of the influence of axial rotation of the transducer membrane on the urethral pressure profile measurements was carried out in twenty women who were on low dose oral contraceptives No influence of low dose oral contraceptives on the urethral pressure profile measurements could be detected When serial urethral pressure profiles were recorded within the same study session, the lowest values for the urethral closure pressure were generally observed in the third and fourth recordings The short term and long term reproducibility were the same for the measurements in the supine and sitting positions
Rotation of the transducer membrane and the position of the study subject significantly influenced the urethral pressure profile The recordings in which the transducer was oriented ventrally showed a shorter urethral length and a higher closure pressure than those in which the pressure transducer was oriented laterally or dorsally Irrespective of the position of

the catheter, all urethral pressure profile variables increased when the subject changed from the supine to the sitting position The increase in urethral closure pressure was most obvious in the distal part of the functional urethra

CHAPTER 6 describes the relationship between hormonal changes during the menstrual cycle and the urethral pressure profile

The influence of endogenous gonadal steroids on the urethral pressure profile was evaluated in 27 healthy nulliparous women with normal ovulatory cycles Simultaneous urethrocystometry was performed in the follicular phase, at midcycle, and early and late in the luteal phase At each study session, serum levels of 17β-estradiol (E_2), progesterone (P), follicle-stimulating hormone (FSH), luteinizing hormone (LH) and prolactin were measured in order to confirm a normal ovulatory pattern for that cycle and for comparison with the urethral pressure profile variables The results of the study demonstrated that the urethral pressure profile shows a consistent pattern at different times during the menstrual cycle Values of the urethral pressure measurements did not change systematically with the hormonal alterations Consequently, there was no evidence that changes in urethral pressures were correlated with variations in E_2 and P levels observed during the menstrual cycle At midcycle and early in the luteal phase, however, the anatomic and functional lengths of the urethra were consistently increased over those found in the early follicular and late luteal phase The data suggest a causal relationship between the changes in serum E_2 concentrations and the changes in urethral length The increase in serum levels of E_2 during the menstrual cycle was also paralleled by an increase in amplitude of the vascular pulsations in the urethral wall With the exception of a positive relationship between weight and anatomic urethral length, neither the weight nor the height of the woman seems to be correlated with the variables of the urethral pressure profile The reproducibility of the urethral pressure measurements during the menstrual cycle was almost similar to that obtained during the pill cycle The greater variability of the urethral length measurements observed during the menstrual cycle can be accounted for on the changing levels of circulating estrogens

CHAPTER 7 describes the influences of pregnancy and delivery on the urethral pressure profile

Simultaneous urethrocystometry was performed serially at 8, 16, 28, and

36 weeks of pregnancy and at 8 weeks post partum in 43 healthy nulli parous women The variables of the urethral pressure profile at rest and the effect of stress (cough) on the urethral pressure profile during pregnancy and after delivery were measured At each study session, blood was obtained for determination of 17β-estradiol (E_2), progesterone (P), and 17-α-OH progesterone (17-OH P)

The results of this study demonstrated that the continence parameters, i e., functional urethral length, urethral closure pressure and integrated pressure, as well as the urethral closure pressure response to stress, did not change systematically during the course of pregnancy Engagement of the presenting part at 36 weeks did not influence the urethral pressure profile measurements Alterations in hormone levels during pregnancy were not correlated with the changes in the urethral pressure profile variables Both urethral pressure and length variables were notably decreased 8 weeks post partum in all women who underwent vaginal delivery when compared with early pregnancy values and with values obtained in the group of healthy nulliparous women in the follicular phase of the menstrual cycle (see Chapter 6) The decrease in length variables was not observed in the six women in whom delivery was by cesarean section The postpartum changes were not significantly correlated with the duration of the second stage of labour nor with the presence or absence of an episiotomy Also, no relationship with infant birth weight was found Values of the urethral pressure profile variables below the median value and defective transmission of pressure over the urethra were observed in almost all women who experienced stress incontinence during pregnancy and/or after delivery These observations suggest that an inherent weakness of the urethral sphincter mechanism plays a key role in the pathogenesis of stress incontinence Vaginal delivery results in a further decrease in urethral closure function

Samenvatting

Het in dit proefschrift beschreven onderzoek werd verricht teneinde de invloeden na te gaan welke biologische variabelen en fysiologische veranderingen bij de vrouw uitoefenen op het drukprofiel van de urethra

Het urethra drukprofiel (UPP) is een grafische weergave van het drukverloop over de gehele lengte van de urethra tijdens de vulfase van de blaas Registratie van het UPP heeft in de laatste twee decennia een belangrijke plaats verworven bij de bestudering van het sfincter mechanisme van de urethra en aanzienlijk bijgedragen tot het verkrijgen van beter inzicht in de fysiologie van continentiemechanisme en mictieproces. Voor de registratie van het UPP wordt in toenemende mate gebruik gemaakt van microtransducers, welke in staat zijn snel en nauwkeurig drukvariaties *in vivo* te meten Door gebruik te maken van twee microtransducers, gemonteerd in een catheter op 6 cm afstand van elkaar, is het mogelijk gelijktijdig de intravesicale druk en het drukverloop in de urethra (UPP), d i simultane urethrocystometrie, te meten

Het eerste gedeelte van dit proefschrift bevat een overzicht van de anatomie en neurofysiologie van blaas en urethra en een beschrijving van het UPP In het tweede deel wordt het eigen onderzoek beschreven

Hoofdstuk 1 geeft een overzicht van de anatomie van blaas en urethra

De wand van blaas en urethra is opgebouwd uit drie spiergroepen, te weten de blaasspier of M detrusor, de trigonale musculatuur en de musculatuur van de urethrawand Voor een beter inzicht in de complexe samenhang tussen deze spiergroepen is een korte beschrijving van de embryologische ontwikkelingsstadia gegeven Recent morfologisch en histochemisch onderzoek toont aan dat de blaasspier en de musculatuur van de urethra anatomisch verschillende spiergroepen vormen De blaasspier is opgebouwd uit een netwerk van gladde spierbundels van verschillende dikte welke nauw met elkaar zijn verweven De gladde musculatuur van de

urethrawand bestaat uit kleinere spierbundels omgeven door compact fibro-elastisch bindweefsel Met betrekking tot oorsprong en verloop van de spierbundels in blaashals en proximale urethra bestaat tussen de verschillende onderzoekers geen eenstemmigheid
De buitenste spiermantel van de urethra wordt gevormd door dwarsgestreepte spiervezels, welke de urethra aan de ventrale en laterale zijde hoefijzervormig omgeven Deze dwarsgestreepte spiermantel is morfologisch verschillend en anatomisch gescheiden van de dwarsgestreepte musculatuur van de bekkenbodem welke de urethra in haar distaal verloop omgeeft De pubourethrale banden, verlopend van het os pubis naar de voorste urethrawand, vormen het ophangmechanisme van de urethra en dragen ertoe bij dat de urethra in haar verloop in het kleine bekken blijft gefixeerd

Hoofdstuk 2 geeft een beschrijving van de neurofysiologie van de lagere urinewegen

Onze kennis omrent de rol van het autonome zenuwstelsel bij de regulatie van het continentiemechanisme en het mictieproces berust voornamelijk op resultaten van fysiologische en farmacologische onderzoekingen Neurohistochemisch en electronenmicroscopisch onderzoek hebben in de laatste twee decennia beter inzicht verschaft in het voorkomen en de verdeling van de verschillende typen zenuweindigingen in blaas en urethra De preganglionaire parasympathische en pre- en postganglionaire sympathische zenuwvezels eindigen in de autonome ganglia in de plexus pelvicus en plexus vesicalis Vanuit deze plexus innerveren postganglionaire zenuwvezels de blaas en urethra De M detrusor wordt geinnerveerd door parasympathische zenuwvezels via de nn pelvici Het aantal parasympathische zenuweindigingen neemt bij de mens in het trigonum en in de urethra geleidelijk af In overeenstemming hiermede zijn de klinische bevindingen, welke wijzen op een ondergeschikte rol van de cholinerge innervatie van blaashals en urethra
De sympathische zenuwen bereiken de lagere urinewegen via de nn hypogastrici Het voorkomen en de verdeling van noradrenerge zenuweindigingen in blaas en urethra is spaarzaam vergeleken met de cholinerge innervatie van deze organen Klinisch en farmacologisch onderzoek, echter, toont aan dat het sympathisch systeem een belangrijke rol speelt bij de innervatie van de lagere urinewegen bij de mens. De aanwezigheid van beta adrenerge receptoren kan worden aangetoond in de detrusor, terwijl in het trigonum en in de wand van de urethra de aanwezigheid van

alpha adrenerge receptoren overheerst Het werkingsmechanisme van het sympathisch systeem op blaas en urethra is niet volledig bekend Het voorkomen van noradrenerge zenuweindigingen op het postganglionaire para sympathische neuron en het bestaan van interganglionaire zenuwverbindingen wijzen op een wederzijdse beinvloeding van het sympathisch en parasympathisch systeem bij de innervatie van de lagere urinewegen
Door interactie met het receptor-molecuul in de targetcel kunnen gonadale steroiden impulsoverdracht in het adrenerge systeem beinvloeden
Er bestaat geen eenstemmigheid met betrekking tot de perifere innervatie van de dwarsgestreepte musculatuur in de wand van de urethra. De dwarsgestreepte musculatuur in de bekkenbodem wordt geinnerveerd via de nn. pudendi
De nn pelvici, de nn hypogastrici en de nn pudendi zijn gemengde zenuwen d w z zij bevatten zowel afferente als efferente zenuwvezels De afferente zenuwvezels schakelen over op het perifeer motorisch neuron en op interneuronen in het ruggemerg, terwijl sommige zenuwvezels rechtstreeks opstijgen naar de hersenstam Binnen het centrale zenuwstelsel bestaat een complex systeem van centripetale en centrifugale zenuwbanen, welke ons in staat stelt de reflexmechanismen in het ruggemerg bewust te beinvloeden Het complexe systeem van zenuwbanen, dat binnen het centrale zenuwstelsel het functioneren van blaas en urethra coordineert, is om redenen van duidelijkheid gerangschikt in 4 neuroanatomische eenheden

Hoofdstuk 3 geeft een beschrijving van het urethra drukprofiel (UPP)

De verschillende technieken, welke worden gebruikt voor het registeren van het UPP, worden vermeld, gevolgd door een korte beschrijving van de betekenis van het registreren van het UPP in de klinische praktijk
De variabelen van het UPP, gedefinieerd volgens de aanbevelingen van de International Continence Society, en de toegevoegde variabelen, gemeten in deze studie, worden beschreven
Tijdens de vulfase van de blaas is de urethra een over haar gehele lengte gesloten tubulaire structuur Continentie berust derhalve op het gesloten zijn van de urethrovesicale overgang en wordt bewerkstelligd door de tonus van het gladde spierweefsel en omgevend fibro-elastisch weefsel in de blaashals en proximale urethra intern of proximaal spfincter mechanisme In het midden en het distale deel van de urethra wordt de urethrale afsluitdruk bepaald door de tonus van de gladde en dwarsgestreepte musculatuur in de wand van de urethra en de dwarsgestreepte muscula-

tuur in de bekkenbodem extern of distaal sfincter mechanisme De binnenste laag van de urethra, opgebouwd uit mucosa en submucosa vormt een sponsachtige, gemakkelijk vervormbare structuur en draagt onder invloed van uitwendige compressie bij tot adequate afsluiting van het lumen van de urethra
Tijdens stress (bv hoesten) en lichamelijke inspanning wordt de intra-abdominale drukverhoging gelijktijdig geheel of nagenoeg geheel overgebracht op de blaas en op het intra-abdominaal gelegen deel van de urethra, zodat een positieve afsluitdruk van de urethra gehandhaafd blijft Actief aanspannen van de dwarsgestreepte spiervezels in de wand van de urethra en de bekkenbodem leidt tot verdere toename van de urethrale weerstand

In HOOFDSTUK 4 worden de doelstellingen van het onderzoek en de toegepaste onderzoeksprocedure beschreven

Deze studie had tot doel een onderzoek naar de variabiliteit van het UPP bij gezonde vrouwen in de geslachtsrijpe periode Meettechnische aspecten van het registreren van het UPP in vivo, zoals reproduceerbaarheid van de meettechniek, effecten van houdingsverandering en rotatie van de catheter evenals de invloeden van lengte en gewicht van de vrouw op het UPP werden onderzocht
Het onderzoek naar de invloed van fysiologische veranderingen betrof de invloed van hormonale veranderingen tijdens gebruik van orale contraceptiva en in de loop van de menstruele cyclus en de invloed van zwangerschap en bevalling
Simultane urethrocystometrie geschiedde met twee microtransducers, gemonteerd in een semiflexibele dacroncatheter. Het meetinstrument, de ijkingsprocedure en de meettechniek worden beschreven Alle registraties werden verricht volgens een gestandaardiseerd onderzoeksprotocol bij gezonde vrouwen in de leeftijd van 18 tot 35 jaar Tijdens iedere onderzoekssessie werd bloed afgenomen voor hormoonbepalingen De variabelen van het UPP werden gecorreleerd met de serumspiegels van 17β-oestradiol en progesteron op het tijdstip van onderzoek De bepalingsmethoden van de serumspiegels van 17β oestradiol, progesteron, prolactine, FSH, LH en 17α-hydroxyprogesteron worden in het kort beschreven

HOOFDSTUK 5 beschrijft de reproduceerbaarheid van de metingen van het UPP met de microtransducer techniek bij gezonde jonge vrouwen

De reproduceerbaarheid van de metingen binnen dezelfde onderzoeks-

sessie (short term reproducibility) en het onderzoek naar de meest betrouwbare meting van het UPP in rust werd verricht bij 12 vrouwen De laagste waarden voor de urethra afsluitdruk werden in het algemeen gevonden in de 3e en 4e registratie
De reproduceerbaarheid van de metingen over verschillende onderzoekssessies (long term reproducibility) evenals de invloed van rotatie van de catheter op de metingen werd onderzocht bij 20 vrouwen, die orale contraceptiva gebruikten Een merkbare invloed van orale contraceptiva op de metingen van het UPP kon niet worden aangetoond
De short en long term reproducibility waren praktisch gelijk zowel voor de registraties in liggende als in zittende houding Rotatie van de catheter en de positie van de onderzoekspersoon beinvloedden op significante wijze de metingen van het UPP De registraties waarbij de transducer ventraal is gericht vertoonden een kortere urethralengte en hogere afsluitdruk dan de registraties met de transducer in laterale resp dorsale positie Bij houdingsverandering, vanuit de liggende in zittende houding, namen alle variabelen van het UPP toe De toename was het duidelijkst voor de afsluitdruk in het distale deel van de functionele urethra

Hoofdstuk 6 beschrijft de invloed van hormonale veranderingen in de loop van de menstruele cyclus op het UPP

De invloed die gonadale endogene steroiden uitoefenen het UPP werd onderzocht bij een groep van 27 gezonde nulliparae met een normale menstruele cyclus Simultane urethrocystometrie werd uitgevoerd op 4 tijdstippen tijdens dezelfde menstruele cyclus vroeg-follicular, peri-ovulatoir, vroeg-luteaal en laat-luteaal Tijdens iedere onderzoekssessie werden de serumspiegels bepaald van 17β-oestradiol (E_2), progesteron (P), FSH, LH en prolactine, zodat het normale ovulatoire patroon van de cyclus door hormoonbepalingen kon worden bevestigd Tevens konden de bepalingen van het UPP worden gecorreleerd met veranderingen in serumspiegels van 17β-oestradiol en progesteron in de loop van de menstruele cyclus
De registratiepatronen van het UPP, geregistreerd op 4 onderzoekstijdstippen bij dezelfde patiente, waren identiek Er bestaat geen aanwijzing dat de afsluitdruk in de vrouwelijke urethra wordt beinvloed door veranderingen in de oestrogeen resp progesteronconcentraties zoals deze voorkomen in de loop van de menstruele cyclus Echter in de peri-ovulatoire en vroeg-luteale phase was de lengte van de urethra, zowel functioneel als anatomisch, langer dan in de vroeg follicularire en laat-luteale phase De bevindingen tonen een verband tussen veranderingen in urethralengte en

variaties in bloedspiegels van 17β oestradiol (Kendall toets voor rangcorrelatie $P < 0.05$) Eveneens kon een toename worden waargenomen in de amplitudo van de vasculaire pulsaties in de wand van de urethra bij toenemende serumspiegels van 17β-oestradiol
Lengte en gewicht van de vrouw lijken niet van invloed te zijn op de variabelen van het UPP Een uitzondering wordt gevormd door een positief verband tussen gewicht en anatomische lengte van de urethra De reproduceerbaarheid van de drukmetingen in de urethra in de loop van de menstruele cyclus was identiek aan die tijdens gebruik van orale contraceptiva De grotere spreiding van de lengte metingen moet worden toegeschreven aan de veranderingen in serumspiegels van 17β-oestradiol tijdens de menstruele cyclus

Hoofdstuk 7 beschrijft de invloed van zwangerschap en bevalling op het UPP

De invloed van zwangerschap en bevalling op de afsluitfunctie van de urethra is onderzocht in een prospectieve studie bij 43 gezonde nulliparae Simultane urethrocystometrie werd uitgevoerd op 4 tijdstippen gedurende de zwangerschap en wel in de 8e, 16e, 28e en 36e zwangerschapsweek en $\pm$ 8 weken na de bevalling De variabelen van het UPP en de urethrale afsluitdruk tijdens stress (hoesten) werden geregistreerd zowel in de liggende als in zittende houding Tijdens ieder onderzoekstijdstip werd bloed afgenomen ter bepaling van 17β-oestradiol (E_2), progesteron (P) en 17α-OH-progesteron (17-OH-P)

Veranderingen tijdens de zwangerschap de resultaten van deze studie toonden aan dat het continentiemechanisme, gevormd door blaashals en functionele urethra, niet wezenlijk verandert onder invloed van de zwangerschap en de daarbij optredende mechanische en hormonale veranderingen Ook het al of niet ingedaald zijn van het voorliggend deel in de 36e zwangerschapsweek had geen duidelijke invloed op de variabelen van het UPP Transmissie van intra abdominale drukverhoging (hoesten) op de blaas en op het intra abdominaal gelegen deel van de urethra blijkt bij iedere vrouw volgens een voor de betreffende vrouw karakteristiek patroon te verlopen en wordt niet in belangrijke mate door de zwangerschap beinvloed

Veranderingen na de bevalling bij alle vrouwen, die langs vaginale weg waren bevallen, waren zowel de urethrale druk als de urethrale lengte

variabelen significant afgenomen ten opzichte van de waarnemingen verkregen vroeg in de zwangerschap en ten opzichte van de waarnemingen verkregen bij gezonde nulliparae in de folliculare fase van de menstruele cyclus (Hoofdstuk 6). De grootte van de afname bleek niet te worden beïnvloed door de duur van de uitdrijvingsperiode, noch door de grootte van het kind, terwijl het al of niet plaatsen van een episiotomie evenmin effect had op de afname van het UPP. Echter bij die vrouwen, die bevielen door middel van keizersnede, uitgevoerd als primaire sectio of in het begin van de ontsluitingsfase, werd een dergelijke afname van de urethrale lengte variabelen niet waargenomen.

Stressincontinentie tijdens zwangerschap en/of na de bevalling werd waargenomen bij die vrouwen, die reeds vroeg in de zwangerschap een verlaagde afsluitdruk van de urethra en onvolledige transmissie van intra-abdominale druk over het proximale deel van de urethra vertoonden. Op basis van deze bevindingen lijkt het gerechtigd te stellen dat een predispositie ofwel intrinsieke zwakte van het sfinctermechanisme van de urethra ten grondslag ligt aan het optreden van stressincontinentie. Vaginale bevalling leidt tot verder functieverlies van het urethra sfinctermechanisme.

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Curriculum vitae

De schrijver van dit proefschrift werd op 15 januari 1941 geboren te 's-Hertogenbosch Hij behaalde het diploma gymnasium-alpha in 1959 aan het St Janslyceum te 's Hertogenbosch en studeerde geneeskunde aan de Rijks Universiteit te Utrecht, waar hij in 1969 zijn arts-examen behaalde In het kader van de voorbereiding tot uitzending naar Ontwikkelingslanden was hij van 1969 tot 1971 als arts assistent werkzaam in achtereenvolgens het St Jozef Ziekenhuis te Gouda (Interne Geneeskunde 3 maanden), Ziekenhuis St Joannes de Deo te Haarlem (Chirurgie 12 maanden), St Lukas Ziekenhuis te Amsterdam (Verloskunde en Gynaecologie 6 maanden) en Tropencursus voor artsen, KIT te Amsterdam Van 1971 tot 1974 werkte hij als District Medical Officer in Zambia, Kashikishi Hospital
In juli 1974 begon hij zijn opleiding tot vrouwenarts op de afdeling Verloskunde en Gynaecologie van het St Canisius Ziekenhuis te Nijmegen (hoofd A-opleiding Dr A J J de Bruin) Ter voltooiing van zijn opleiding was hij vanaf 1 juli 1978 werkzaam in de Universiteitskliniek voor Gynaecologie en Verloskunde van het St Radboud Ziekenhuis te Nijmegen (Hoofden Prof Dr J L Mastboom en Prof Dr T K A B Eskes) Op 1 juli 1979 werd hij als specialist geregistreerd Hij bleef als Chef de Policlinique aan de afdeling Gynaecologie en Verloskunde van het St Radboud Ziekenhuis verbonden tot 1 januari 1982 Sinds januari 1982 is hij als vrouwenarts gevestigd in het St Anna Ziekenhuis te Oss in associatief verband met Dr V G H J Kirkels en G F M van der Velden Tevens is hij als part-time wetenschappelijk medewerker verbonden aan de R U L , Ziekenhuis St Annadal, Maastricht

Stellingen

BEHOREND BIJ HET PROEFSCHRIFT

THE URETHRAL PRESSURE PROFILE IN CONTINENT WOMEN

J. M. VAN GEELEN

I

Simultane urethrocystometrie is een waardevolle aanwinst bij de diagnostiek van urine incontinentie bij de vrouw

II

De vrouwelijke urethra is een oestrogeen gevoelig orgaan *(Dit proefschrift)*

III

Vaginale bevalling leidt tot functieverlies van het urethra sfincter mechanisme De afname in urethra sfincter functie wordt niet beinvloed door de duur van de baring, noch door de grootte van de pasgeborene, noch door het al of niet plaatsen van een episiotomie *(Dit proefschrift)*

IV

Het therapeutisch effect van een geslaagde anti-incontinentie operatie berust niet zozeer op verhoging van de urethrale weerstand, doch op verbetering van de transmissie van de verhoogde intra abdominale druk

V

De betere overeenkomst van het klaringsprofiel van haemodiafiltratie met de natuurlijke nierfunctie en de uitstekende tolerantie maken haemodiafiltratie tot de beste keuze uit de diverse kunstnierbehandelingen.

(J A van Geelen Proefschrift Maastricht 1983)

IV

Umbilicale paraaortale bypass en blokresectie van de rechter leverkwab vormen de operatie van keuze bij het carcinoom van de ductus hepaticus

(E J Boerma Proefschrift Nijmegen 1983)

VII

De diagnose ,,abortus completus'' is incompleet, indien niet gevolgd door curettage van het cavum uteri en patholoog anatomisch onderzoek van het curettement

VIII

Initiele orale therapie met β-sympathicomimetica bij dreigende vroeggeboorte is niet effectief *(D A Smit Proefschrift Maastricht 1983)*

IX

Gebruik van orale contraceptiva vermindert de kans op optreden van ontsteking in het kleine bekken

X

De traditionele gezondheidsmaten vormen geen maatstaf voor de kwaliteit van de gezondheidszorg *(Huisarts en Wetenschap 1982)*

XI

Les hommes font les lois, les femmes font les mœurs